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Role Of The Dorsal Striatum In Learning and Decision Making

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Abstract

The striatum, the input region of the basal ganglia, has been shown to mediate many cognitive functions. The striatum itself can be functionally segregated into dorsal (DS) and ventral striatum (VS). For more than 60 years, DS has been reported to mediate stimulus-response learning, though evidence has been accruing pointing to a role in decision making. These literatures have been growing independently and an aim of this thesis was to bridge these two bodies of knowledge. We directly investigated the role of DS in stimulus-response learning versus decision making using functional magnetic resonance imaging (fMRI) in patients with Parkinson's disease (Chapter 2) and obsessive compulsive disorder (Chapter 3). In Chapter 4, the role of DS in stimulus-response habit learning was tested in healthy individuals using fMRI. In three separate experiments (Chapters 2-4), all of the results strongly support the notion that DS mediates decision making and not learning. DS is implicated in many disorders ranging from Parkinson's disease, obsessive compulsive disorder and addiction, and clarifying the role of DS in cognitive function is paramount for understanding substrates of disease and developing treatments.

Keywords

Striatum; Stimulus-response Learning; Parkinson's disease; Obsessive compulsive disorder; functional MRI.

Co-Authorship Statement

I was responsible for all aspects of the experiments conducted in Chapters 2-4. I did receive assistance in the following capacities:

In Chapter 2, Penny A. MacDonald and Ken N. Seergobin assisted with project design. Dan Mendonça and Mary E. Jenkins provided assistance with patient recruitment. Ken N. Seergobin provided assistance with data analysis. Adrian M. Owen, Hooman Ganjavi, Mary E. Jenkins, and Penny A. MacDonald assisted with manuscript editing.

In Chapter 3, Penny A. MacDonald and Ken N. Seergobin assisted with project design. Mark Watling assisted with patient recruitment. Marc Watling provided assistance with patient recruitment. Marc Lawrence assisted with data collection. Ken N. Seergobin assisted with data analysis. Marc Lawrence, Mark Watling, Adrian M. Owen, and Penny A. MacDonald assisted with manuscript editing.

In Chapter 4, Penny A. MacDonald and Ken N. Seergobin assisted with project design. Ken N. Seergobin provided assistance with data analysis. Adrian M. Owen, and Penny A. MacDonald assisted with manuscript editing.

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List of Abbreviations

3T	3 Tesla
ANART	National Adult Reading Test
ANOVA	Analysis of Variance
BAI	Back Anxiety Inventory
BDI-II	Beck Depression Inventory
BG	Basal Ganglia
BOLD	Blood Oxygenation Level Dependent
CBT	Cognitive Behavioural Therapy
COMT	Catechol-O-methyltransferase
COVIS	Competition between Verbal and Implicit Systems
CTRL	Control
DA	Dopaminergic Therapy
DAT	Dopamine Transporter
DLS	Dorsolateral Striatum
DLPFC	Dorsolateral Prefrontal Cortex
DMS	Dorsomedial Striatum
DRD	Dopamine Receptor
DS	Dorsal Striatum
DSM	Diagnostic and Statistical Manual of Mental Disorders

DTI	Diffusion Tensor Imaging
ERP	Exposure and Response Prevention
FB Event	Feedback event
FDR	False Discovery Rate
fMRI	functional Magnetic Resonance Imaging
FWE	Family-Wise Error
GABA	γ -aminobutyric acid
GLM	General Linear Model
ISI	Inter-stimulus Interval
ITI	Inter-trial Interval
ι -dopa	ι -3,4-dihydroxyphenylalanine
LED	ι -dopa Equivalent Dose
MATLAB	Matrix Laboratory
M1	Primary Motor Cortex
MNI	Montreal Neurological Institute
MoCA	Montreal Cognitive Assessment
MSN	Medium Spiny Neuron
NAcc	Nucleus Accumbens
OCD	Obsessive Compulsive Disorder
OFC	Orbitofrontal Cortex

PD	Parkinson's Disease
PET	Positron Emission Tomography
ROI	Region of Interest
RT	Response Time
SD	Standard Deviation
SEM	Standard Error of the Mean
SERT	Serotonin Transporter
SNc	Substantia Nigra pars compacta
SPEED	Subcortical Pathways Enable Expertise Development
SPM	Statistical Parametric Mapping
SR Event	Stimulus-Response Decision
SSRI	Selective Serotonin Reuptake Inhibitor
UPDRS	Unified Parkinson's Disease Rating Scale
VLPFC	Ventrolateral Prefrontal Cortex
VS	Ventral Striatum
VTA	Ventral Tegmental Area
YBOCS	Yale-Brown Obsessive Compulsive Scale

Chapter 1

1 Literature Review

1.1 Striatum and the Basal Ganglia

The basal ganglia (BG) are a collection of sub-cortical nuclei responsible for the generation of motor movements, and increasingly, in cognitive functions (Grahn, Parkinson, & Owen, 2009; Monchi, Petrides, Petre, Worsley, & Dagher, 2001). The BG are comprised of four interconnected structures: the striatum, globus pallidus, substantia nigra (SN), and subthalamic nucleus (Alexander, DeLong, & Strick, 1986; Bonelli & Cummings, 2007).

The striatum is the main input nuclei, receiving glutamatergic afferents from all cortical areas except for primary visual and primary auditory cortices, as well as dopaminergic afferents from SN pars compacta (SNc) and ventral tegmental area (VTA). Striatal efferents project to either the internal globus pallidus (i.e., *direct* pathway) or to the external globus pallidus; which, in turn, projects to the subthalamic nucleus and then the internal globus pallidus (i.e., *indirect* pathway). Subsequently, both pathways project to the thalamus; which, in turn, project to the cortex (Koob, Balcom, G.J., Meyerhoff, & Meyerhoff, 1975). An illustration of the basic cortico-basal ganglia-thalamocortical circuit is presented in Figure 1.1. One of the functions of dopamine in the striatum is to regulate the balance between the indirect, and the direct pathways (Newton & Price, 1975).

The role of dopamine in balancing between direct and indirect pathways has been modelled by Cohen and Frank (2009) with respect to approach and avoidance learning, also referred to as Go/No-Go learning. Dopamine is viewed as playing a modulatory role in the basal ganglia, interacting with different dopamine receptors that populate the direct and indirect pathways. In the direct pathway, dopamine receptor type 1 and 5 (DRD1 and DRD5, respectively) are expressed and subsequently facilitate an increase in cortical activity (Kravitz, Tye, & Kreitzer, 2012). Conversely, the indirect pathway expresses DRD2, 3, and 4 and activation of this pathway results in attenuated cortical activity (Kravitz et al., 2012). Dopamine pulses that arrive after receiving a reward facilitate activity through the

direct pathway and inhibit the indirect pathway, leading to a Go response. When negative feedback or punishments are received, dopamine levels decrease resulting in activity through the indirect pathway and inhibition of the direct pathway, leading to a No-Go, or absence of that particular response. When the concentration of dopamine is altered greatly, as in Parkinson's disease (PD), a variety of motor and cognitive symptoms develop.

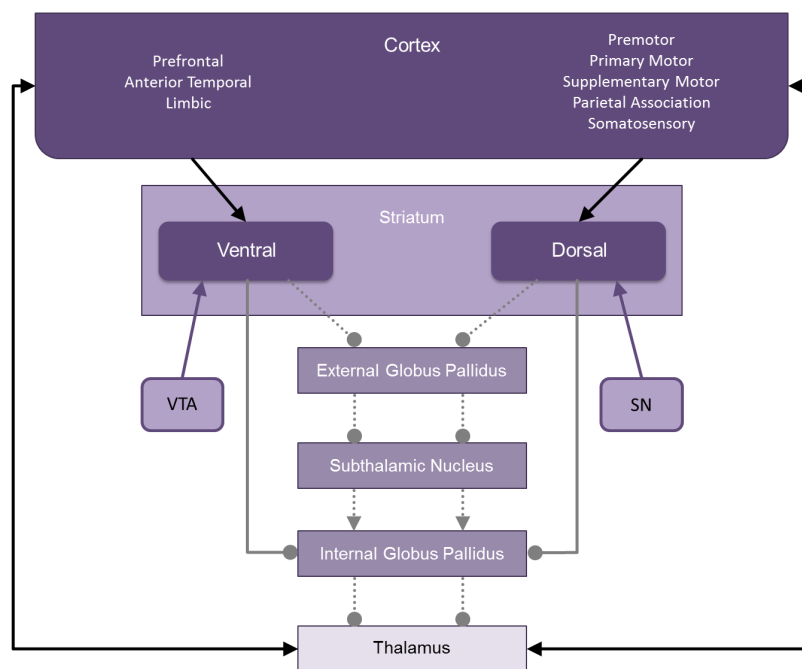


Figure 1.1 Schematic diagram of the basal ganglia and its afferents and efferents

Lines that terminate in arrowheads are excitatory connections; lines that terminate in circles are inhibitory connections; purple lines are dopaminergic connections; grey solid lines represent the *direct* pathway and grey dotted lines represent the *indirect* pathway. VTA – Ventral tegmental area; SN – Substantia nigra.

1.2 Cytoarchitecture of the Striatum

The cytoarchitecture of the striatum is different compared to the other nuclei in the basal ganglia. The most common neuronal type is γ -aminobutyric acid (GABAergic) medium spiny neuron (MSN). These neurons receive inputs from the thalamus and cortex via glutamatergic neurons, dopaminergic afferents from the SNc and VTA, and inter-neuronal connections via GABAergic and cholinergic neurons (Gonzales & Smith, 2015). Whereas

glutamatergic neurons synapse on the dendrites of the MSNs, dopaminergic neurons are uniquely positioned mainly on the necks of MSN dendritic spines (DiFiglia, Pasik, & Pasik, 1978). The location of dopaminergic neurons allows dopamine to modulate the cortico-striatal connections needed for striatum function, such as voluntary motor movements, and reinforcement learning (Ashby, Ennis, & Spiering, 2007; Kravitz et al., 2012). Cholinergic interneurons have recently been under intense investigation. Originally thought to just be a class of tonically-active neurons with no behavioural role (M. Kimura, Rajkowski, & Evarts, 1984), the current hypothesis indicates a role in responding to salient environmental stimuli. Specifically, the firing frequency of cholinergic neurons decreases in response to salient stimuli (e.g., noxious, rewarding environmental stimuli) and this change in activity may prime MSNs of the presence of the stimulus (Bohnen et al., 2012; Calabresi, Picconi, Parnetti, & Di Filippo, 2006; Gonzales & Smith, 2015). Subsequently, dopaminergic inputs may assign a value to the stimulus (Gonzales & Smith, 2015).

1.3 Divisions of the Striatum

The striatum can be subdivided in many different ways, such as anatomically into the caudate nucleus, putamen, and nucleus accumbens (NAcc), and functionally into dorsal striatum (DS), and ventral striatum (VS; P. A. MacDonald & Monchi, 2011; Wickens, Horvitz, Costa, & Killcross, 2007; see Figure 1.2). A brief discussion of the common divisions is below along with a rationale of our chosen method.

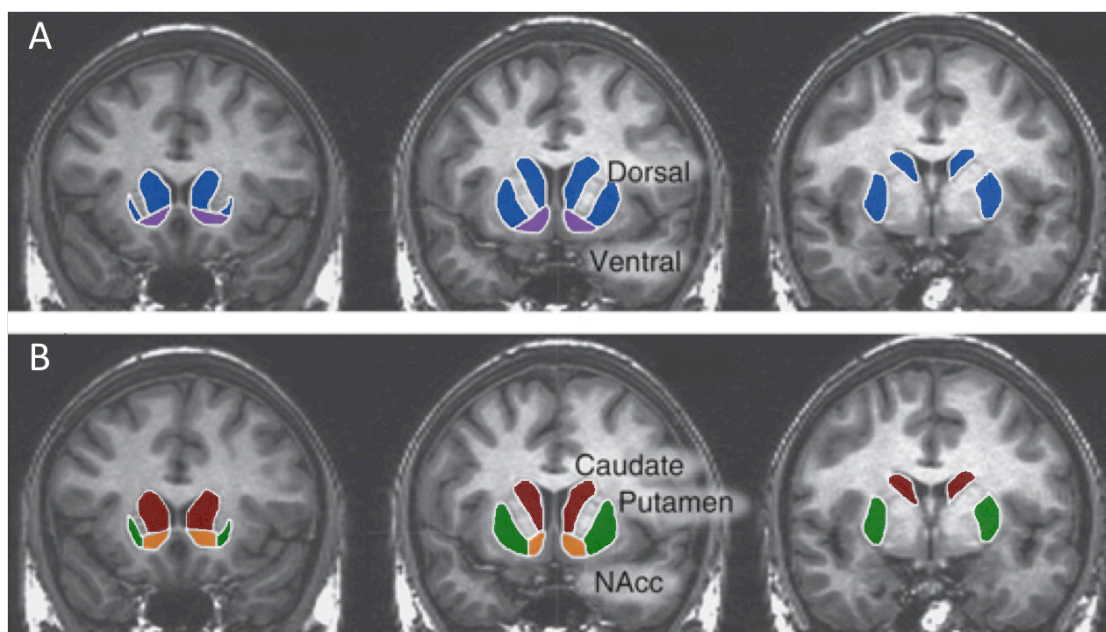


Figure 1.2 The functional and anatomical divisions of the striatum

The striatum can be subdivided functionally and anatomically. **A.** The striatum can be subdivided functionally into the dorsal and ventral striatum. The dorsal striatum is composed of the bulk of the caudate nucleus and putamen, shown in blue, whereas the ventral striatum is composed of ventral aspects of the caudate nucleus, putamen as well as the NAcc. **B.** The anatomical subdivisions of the striatum: caudate nucleus (shown in red), putamen (shown in green), and NAcc (shown in orange). Figure adapted from Haber and Knutson (2010).

1.3.1 Caudate, Putamen, and Nucleus Accumbens

Reported in hundreds of studies over the past 50 years, and represented in most neuroscience and neuroanatomy textbooks, the striatum is said to be composed of two structures, the caudate nucleus and putamen (G E Alexander, M R DeLong, & Strick, 1986; Hewitt, 1961; Künzle, 1975). Occasionally, the NAcc is also included in the striatum proper (Szabo, 1980; Voorn, Vanderschuren, Groenewegen, Robbins, & Pennartz, 2004). In humans and non-human primates, the caudate nucleus appears to be anatomically separated from the putamen by a large bundle of ascending axons called the internal capsule (see Figure 1.2). There is no gross anatomical division between the caudate nucleus and putamen, and the NAcc but it is generally denoted as the region that connects the caudate

and putamen located inferior to the internal capsule (P. A. MacDonald et al., 2011; Postuma & Dagher, 2006; Voorn et al., 2004).

From the work of Künzle, DeLong and Alexander in the 1970's and 1980's, we began to understand that the striatum is organized into semi-discrete cortico-basal ganglia-thalamocortical circuits, each responsible for a different function (G E Alexander et al., 1986). Künzle (1975) used autoradiography in adult monkeys to trace axonal pathways from the cortex to the striatum. Specifically, radiolabeled amino acids were injected into specific areas of the primary motor cortex (M1) and the axon terminals within the caudate nucleus and putamen were visualized and mapped. Künzle (1975) found that nearly all projections from M1 terminated in the putamen and were topographically organized, such that neurons originating from the face region of M1 were mapped separately from those originating from the leg-tail region of M1. Additionally, there was very little input to the caudate nucleus, supporting the notion of an anatomically separate caudate and putamen.

Alexander and DeLong (1985) used microstimulation to identify connections between the striatum and cortex. Neurons within the caudate and putamen were stimulated and motor responses were measured in awake monkeys. They replicated Künzle in showing the topographic map of the putamen resulting in motor movements. Interestingly, stimulating the caudate did not result in any motor movement. Similar stimulations were conducted on other areas of the caudate nucleus, putamen and NAcc resulting in five non-overlapping functional loops: motor, oculomotor, dorsolateral prefrontal, lateral orbitofrontal, and anterior cingulate. The motor loop passed through the putamen, oculomotor, dorsolateral prefrontal and lateral orbitofrontal traversed through different areas of the caudate nucleus, and the anterior cingulate loop included the NAcc (G E Alexander et al., 1986). The lack of overlap between the circuits resulted in the classification of the caudate nucleus, putamen and NAcc as separate structures, anatomically connected to different cortical partners.

The division of the striatum into the caudate nucleus, putamen and NAcc is pervasive; it exists in many current textbooks such as the recently published 5th edition of *Principles of Neural Science* (Kandel, Schwartz, Jessell, Siegelbaum, & Hudspeth, 2013) but it may not

be the most apt division. This division begins to break down in recent studies utilizing modern neuroimaging techniques and diffusion tensor imaging (DTI) that show functional divisions may not be separated by the internal capsule but rather follow a ventromedial to dorsolateral gradient where the same functional loop can implicate both the caudate nucleus and putamen (Choi, Yeo, & Buckner, 2012; Tziortzi et al., 2014; see Section 1.2.3 below).

1.3.2 Dorsomedial and Dorsolateral Striatum

In rodents, distinctions between caudate nucleus and putamen are not typically made as these regions merge into one another and form a unitary structure referred to as DS (Voorn et al., 2004), and VS is typically defined as the NAcc (Burton, Nakamura, & Roesch, 2015). Instead, divisions are made along the anterior to posterior, and medial to lateral axes and are based on function rather than anatomy (Burton et al., 2015). For example, dorsal medial striatum (DMS) is often reported to mediate early, goal directed learning, whereas dorsal lateral striatum (DLS) is recruited during habit learning (Yin & Knowlton, 2006). Learning is a main focus of this thesis and will be defined later on.

In the rodent literature, NAcc is often reported to respond to the value of an outcome. Specifically, neurons in the NAcc will increase firing frequency when presented with a high value reward and will reduce activity when faced with a small reward or punishment (Burton et al., 2015). This change in firing frequency of the NAcc is utilized by DMS in goal-directed learning (Burton et al., 2015; Wolfram Schultz, 1998; W. Schultz, Apicella, Scarnati, & Ljungberg, 1992).

1.3.3 Dorsal and Ventral Striatum

In humans, caudate and putamen appear to be separate structures and many studies report these two regions perform different functions (Chiu, Jiang, & Egner, 2017; Minoru Kimura, 1992; Rolls, Thorpe, & Maddison, 1983; Seger & Cincotta, 2005; Thompson, 1959; Thompson RL, 1963; Yanike & Ferrera, 2014), however there is a lot of structural and functional data suggesting the opposite; that these regions are a unitary structure.

If caudate nucleus and putamen were functionally and anatomically separate structures, one would expect non-overlapping cortical, subcortical connections, facilitating the various functions, as we see in other areas with various nuclei like the thalamus (Angeles Fernandez-Gil, Palacios-Bote, Leo-Barahona, & Mora-Encinas, 2010). However, this is not the case. Neuronal connections to and from the striatum are not segregated into caudate and putamen connections, but rather form an anterior to posterior gradient that transcends the internal capsule, the bundle of axons that ‘separate’ the striatum into the caudate and putamen. The anterior to posterior gradient of connectivity has been confirmed by a variety of methods, including DTI and functional connectivity for both cortical connectivity (Choi et al., 2012; Janssen, Jylanki, Kessels, & van Gerven, 2015; Jung et al., 2014; Tziortzi et al., 2014), and brainstem, dopaminergic connectivity (Chowdhury, Lambert, Dolan, & Duzel, 2013; Haber, 2014; Roeper, 2013).

The anterior to posterior pattern of connectivity is highly supported in the literature and there is much overlap between the varying methodologies and tractography seeds used. Generally, areas of the prefrontal and frontal cortex are reciprocally connected to the anterior portions of the striatum (including NAcc, caudate nucleus and putamen) and as you move posteriorly through the striatum, more posterior cortical regions connect to the striatum. Choi et al. (2012) discerned the functional organization of striatal subregions using resting state functional magnetic resonance imaging (fMRI) with 1000 subjects. The authors were able to parcellate the striatum into five distinct networks using cortical seeds chosen from other studies including tractography studies in monkeys. A limbic network that included NAcc and most ventral portions of caudate and putamen, a ventral attention network connected predominantly to anterior putamen, a motor network that concentrated on lateral regions of the posterior putamen, and two association networks (i.e., fronto-parietal and default-mode) that included regions of both caudate nucleus and putamen. The five broad networks, specifically the association networks were then further parcellated into smaller networks. The five networks correlate highly with tractography studies done in monkeys, as well as other methods parcellating the human striatum (Janssen et al., 2015; Jung et al., 2014; Tziortzi et al., 2014).

Studies that report a functional or structural divide between caudate and putamen often examine connectivity using striatal-based (i.e., caudate and putamen derived) seeds (Janssen et al., 2015). Choosing striatal-based seeds biases the results and interpretation towards examining the caudate nucleus and putamen as separate structures. Similar to Choi et al. (2012), Janssen et al. (2015) investigated striatal connectivity using resting state fMRI but chose seeds within caudate nucleus and putamen instead of cortical regions. The six resulting functional subdivisions were divided along the internal capsule into, dorsal caudate, ventral caudate, rostral/caudate accumbens, rostral putamen, caudal putamen, and dorsal putamen. The authors used a correlation matrix to examine inter-hemispheric cluster correlations and similarities between neighbouring clusters. An interesting finding that is not discussed are the intermediate correlations between non-neighbouring clusters. For example, the ventral caudate cluster is moderately correlated with the rostral putamen and dorsal putamen clusters, indicating that they may share aspects of their respective networks. Applying this result to the Choi et al., 2012 framework, the ventral caudate and rostral putamen clusters, together resemble the limbic or default network. Taken together, the literature points more to functional subdivisions that differ on an anterior to posterior axis, rather than a caudate/putamen anatomical axis.

Similar to cortical connections to the striatum, the dopaminergic connectivity also has an anterior to posterior gradient that does not discriminate between caudate and putamen. Haber (2014) reviewed the dopaminergic connectivity to the striatum and their role in integrating information processing across limbic, cognitive and motor functions. The striatum is innervated by dopamine neurons that originate primarily from the SNc and VTA. The VTA and SNc are not wholly separate structures and therefore merge into one another and have overlap in the striatal areas they innervate. VTA-innervated structures consist mainly of VS or the limbic networks (Choi et al., 2012). The SNc can be subdivided into two populations based on the presence of calbindin, a group of calcium-binding proteins. Calbindin-positive dopamine cells are situated in the dorsal aspect of the SNc and merge into the VTA, which are also calbindin-positive. The ventral region of SNc is composed of calbindin-negative dopamine cells. Respectively, these regions of dopamine cells are referred to as dorsal tier and ventral tier SNc cells. The presence or absence of calbindin allows for the visualization of the dorsal and ventral tier SNc neurons and

correlates highly with striatal connectivity. Dorsal tier SNc neurons are reciprocally connected to caudate nucleus and putamen along the middle of the striatum that are part of the association networks. Ventral tier SNc neurons, conversely, are connected to dorsal lateral regions of the striatum, specifically in the motor network (Chowdhury et al., 2013; Haber, 2014).

Interestingly, SNc and VTA have been implicated in reinforcement learning, with SNc involved in response selection and decision-making whereas, VTA is recruited during reward signalling and motivation (Roeper, 2013).

It is based on the dopaminergic segregation of the striatum—VTA innervating ventral areas of the caudate nucleus, putamen and NAcc (i.e., VS), and SNc projecting to the rest of the caudate and putamen (i.e., DS)—that we and others have chosen to divide the striatum (Garrison, Erdeniz, & Done, 2013; Hart, Leung, & Balleine, 2013; Helie, Roeder, & Ashby, 2010; A. A. MacDonald et al., 2014; P. A. MacDonald & Monchi, 2011; J. O'Doherty et al., 2004; Robertson, Hiebert, Seergobin, Owen, & MacDonald, 2015). Anatomically, slight cytoarchitectural differences, as well as divergent glutamatergic afferents, and non-anastomosing blood supplies separate DS and VS. On a macroscopic level, there is no wholly agreed upon point of division. Pragmatic division often use different anatomical landmarks, such as the internal capsule (P. A. MacDonald et al., 2011), or fMRI slices along the *z*-axis have been used (Postuma & Dagher, 2006).

1.4 Dorsal Striatum

1.4.1 Anatomy

DS is comprised of the bulk of the caudate nucleus and putamen and is vascularized by the lateral lenticulostriate arteries, off of the middle cerebral artery (Feekes & Cassell, 2006). The main neuronal type in the striatum is the MSN. Through a wide range of firing frequencies, dopamine stimulation from SNc is rapid and maximal in DS (Wickens et al., 2007; Zhang et al., 2009). This is a result of a high concentration of dopaminergic afferents to these MSNs. Dopamine Transporter (DAT), a membrane-spanning protein responsible for the synaptic clearance of dopamine, is in high abundance in DS, resulting in rapid

clearance, and therefore, short stimulation periods (Wickens et al., 2007). The anatomical makeup of DS, with high concentrations of dopaminergic afferents and DAT, results in almost binary responding, with maximal stimulation at a range of dopamine firing frequencies, followed by rapid clearance of synaptic dopamine. Through reciprocal glutamatergic afferents, DS is connected to the primary, supplementary, and pre-motor cortex, as well as to the dorsolateral prefrontal cortex, parietal association cortex, and somatosensory cortex (Leh, Chakravarty, & Ptito, 2008). As a result of the rapid binary responding of DS, coupled with reciprocal connections to effector areas such as the motor cortex, and dorsolateral prefrontal cortex, it is well-adapted to perform functions such as deciding among alternatives and response selection.

1.4.2 Function

DS has been implicated in a multitude of functions including selective attention (Agnoli & Carli, 2011), both explicit (Benke, Delazer, Bartha, & Auer, 2003) and implicit retrieval (Boyd & Winstein, 2004), complex planning (Su, Chen, Kwan, Lin, & Guo, 2007), and task switching (i.e., switching between response strategies; Aarts et al., 2014; Aarts et al., 2010; Cameron, Watanabe, Pari, & Munoz, 2010). Most notably however, DS has been implicated in learning (Waldschmidt & Ashby, 2011; Yin & Knowlton, 2006), and decision making (Atallah, Lopez-Paniagua, Rudy, & O'Reilly, 2007; Grahm, Parkinson, & Owen, 2008), which will be discussed in depth below.

1.4.3 Dorsal Striatum in Learning

DS has long been implicated in learning situations, both early goal-directed learning (Boettiger & D'Esposito, 2005; Brovelli, Laksiri, Nazarian, Meunier, & Boussaoud, 2008; Delgado, Miller, Inati, & Phelps, 2005; Foerde, Knowlton, & Poldrack, 2006; Brian Lau & Glimcher, 2007; B. Lau & Glimcher, 2008; R. A. Poldrack, Prabhakaran, Seger, & Gabrieli, 1999; Thompson, 1959; Thompson RL, 1963; Xue, Ghahremani, & Poldrack, 2008), and late-stage, habit learning or automaticity (Helie et al., 2010; R. A. Poldrack et al., 2005; Soto, Waldschmidt, Helie, & Ashby, 2013; Yamamoto, Kim, & Hikosaka, 2013; Yin & Knowlton, 2006). Much of the literature implicating DS in learning involves

different versions of a stimulus-response task (explained in depth in 1.6). Briefly, stimulus-response learning is a form of implicit learning where responses (e.g., button presses) are associated, typically through trial and error, with a certain stimulus (e.g., abstract image). Stimulus-response learning typically involves reinforcement learning or instrumental conditioning. Below is an in-depth discussion of several models implicating DS in learning.

1.4.3.1 DMS- and DLS-mediated Learning

Briefly discussed in section 1.3.2, DMS- and DLS-mediated learning theories originated in the rodent literature and have subsequently been investigated in humans. Experiments often involved lesioning areas of DMS or DLS of rodents and investigating subsequent impairments on goal-directed or habit learning. This theory ascribes early, goal-directed learning to DMS with the bulk of later-stage learning occurring in DLS, during which habits are formed (Hernandez, Redgrave, & Obeso, 2015; Liljeholm & O'Doherty, 2012; Macpherson, Morita, & Hikida, 2014; Redgrave et al., 2010; Voorn et al., 2004). Habit learning is variously defined as reflecting stimulus-specific responses that a) persist even when feedback is omitted or is reversed, generalizing across situations (Myers et al., 2003; Shohamy & Wagner, 2008), b) are unaffected by distracting information or tasks (Foerde et al., 2006), and c) interfere with enacting new incongruent responses (C. M. MacLeod & Dunbar, 1988). Roughly, the homologous structures in humans for DMS and DLS are the anterior, dorsomedial DS (i.e., head of the caudate nucleus) and ventromedial prefrontal cortex, versus dorsolateral putamen respectively (Balleine & O'Doherty, 2010; Yin & Knowlton, 2006). Some views further claim that DLS, in addition to being implicated in forming stimulus-response habits, mediates and sustains habitual or automatic responding once these associations are acquired and well entrenched, so-called action control (Balleine & O'Doherty, 2010; Everitt & Robbins, 2005; Tricomi, Balleine, & O'Doherty, 2009) but see (Ashby et al., 2007; Helie et al., 2010).

Many studies in this area aim to differentiate the neural correlates characterizing goal-directed and habit learning. One main technique utilized is outcome devaluation. Adams and Dickinson (1981) trained rats to press a lever by providing them with a sucrose solution

reward after each lever press. After a period of training, lithium chloride, a mild poison resulting in illness, was added to the sucrose solution, devaluing the reward. This led to a reduction in lever pressing until the behaviour was extinguished. The change in behaviour suggests that rats initially learned a lever-press-sucrose association and this association was altered with the addition of illness and the devaluing of the outcome. Learning what actions will most likely yield rewards is termed *goal-directed learning*. Since this form of learning is facilitated through receiving rewards, the learned associations are sensitive to the changing value of the outcome. If the outcome is no longer rewarding the organism will terminate the behaviour (Balleine & O'Doherty, 2010; de Wit, Barker, Dickinson, & Cools, 2011; Redgrave et al., 2010; Yin & Knowlton, 2006). In the same study, Adams and Dickinson (1981) found that outcome devaluation could be influenced by the length of training, such that if the association was overtrained, it was no longer sensitive to devaluation and the rat would continue to press the lever while being made ill. This type of learning is referred to as *habit learning*. The association has progressed beyond the reward, and the response will be continued irrespective of the outcome (Thorndike, 1898; Yin & Knowlton, 2006). Without intervention, stimulus-response learning typically proceeds through a goal-directed learning phase, transitioning into habit learning once the association is overtrained (Yin & Knowlton, 2006).

DMS is reciprocally connected to the prefrontal cortex, specifically the prelimbic region, and lesions of either of these areas abolish goal-directed behaviour in early learning, with animals relying on previously-formed habitual behaviour. Lesions to DLS—a region of the striatum reciprocally connected to areas of the motor and pre-motor cortex—results in an association that is perpetually goal-directed (Yin & Knowlton, 2006) and reliant on outcome information.

Tricomi et al. (2009) investigated the role of DLS in habit learning using humans and fMRI. A free-operant task was developed from rodent literature and involved self-paced button-presses in response to an abstract image. There were two groups, one group received 16 minutes of training and the other group received 48 minutes of training. Briefly, an image would appear on the projection screen that included an abstract image and an indication of what button to press. Participants could press this button as often as desired and after each

button press would appear a grey circle indicating no reward, or an image of an M&M or Frito, indicating a reward. The proportion of rewards given was based on a variable-interval schedule that averaged one reward every 10 seconds. Rewards accumulated during the task were given to the participants after the scanning session. Following training, one food reward was devalued through satiation. Participants were instructed to eat one of the rewards (either M&Ms or Fritos) until further consumption was no longer pleasurable. Subsequently, participants were scanned during an extinction task, identical to the training sessions but no rewards were given. If the stimulus-response associations formed habits, it was expected that the number of button-presses would be similar between the devalued and pleasurable reward. If the associations did not form habits and still exhibited a goal-directed nature, it was expected that participants would make fewer button-press responses for the devalued reward. Participants in the short-training group retained goal-directed behaviour and responded less often to the devalued reward, whereas participants in the long-training group exhibited habitual responding. FMRI data revealed that an area of the ventral putamen, indicated to be a region of the DLS was active more in habitual responders compared to those who were goal-directed, and this activity increased across the training session. The authors concluded that this area in the ventral putamen must be involved in stimulus-response habit learning.

1.4.3.2 COVIS Model

The competition between verbal and implicit systems, or COVIS model, asserts that category learning, another version of stimulus-response learning, involves two competing systems, (1) a verbal system that classifies stimuli into categories that can be verbalized, and (2) an implicit system that uses procedural learning (Ashby, 1998). For example, categorizing rectangles that are taller than they are wide into one category and rectangles that are wider than they are tall into another category, would be an example of a rule that is easily verbalized. Learning in this case is explicit and involves frontal and temporal language areas, among others. Rules that are not easily verbalized tend to involve attributes that differ in units and are therefore difficult to explicitly describe. For example, it would be difficult to verbalize the categories if you need to categorize objects that differ in the diameter of a circle as well as the angle of a radial line that spans the diameter of the circle.

The difficulty arises because circle diameter and line angle have different units. Learning in this latter case is implicit, or procedural and linked to the motor and supplementary motor areas. Both learning systems intersect with DS, and it is here where the competition takes place. Ashby (1998) references the cortico-basal ganglia-thalamocortical circuits and assert that verbal category learning involves a frontal circuit including the frontal language areas, anterior cingulate and prefrontal cortex. The implicit system, rather, is mediated by a striatal loop that passes through the extrastriate visual areas, as well as the prefrontal cortex. In any categorization task, Ashby (1998) contends that only one of the two systems will dominate and the DS is responsible for mediating and switching between the two systems. More importantly, the DS is claimed to mediate the stimulus-response association learning.

1.4.3.3 Actor-Critic Model

The actor-critic model, first hypothesized by Sutton and Barto (1998) and later supported by J. O'Doherty et al. (2004), states that reinforcement learning consists of two separate components, a *critic* which utilizes feedback to learn to predict future rewards, and an *actor* which uses the information from the *critic* to make better decisions. The *critic* uses a prediction error signal generated by the phasic firing of midbrain dopaminergic neurons. A prediction error signal is generated whenever an unexpected reward is given (Rutledge, Dean, Caplin, & Glimcher, 2010; W. Schultz et al., 1992). J. O'Doherty et al. (2004) scanned healthy participants using 3 Tesla (T) MRI while they completed a stimulus-response learning task. The experiment consisted of two tasks, one instrumental and the other Pavlovian. In the instrumental conditioning task, two abstract images appeared on the screen, one left- and the other right-of-centre, and the participant made a button-press response choosing one of the two images. In the reward trials of the task, one image was more likely to produce a juice reward compared to the other and the participants were required to learn the most rewarding images. In the neutral version, the outcome was a neutral solution, not deemed to be rewarding. In the Pavlovian task, the same trial structure was used, however the computer made the responses and the participant indicated which image the computer chose. The rationale for using an instrumental and Pavlovian task was to examine value predictions by the *critic* in the presence (i.e., instrumental task) and

absence (i.e., Pavlovian task) of action selections by an *actor*. The results showed that VS correlated strongly with the prediction error signal in both tasks, whereas DS correlated with prediction error only during the instrumental task. Authors concluded that VS is the *critic*, coding for the prediction error signal and sending this information to the DS, or *actor*, where this information is used to learn the stimulus-response association and perform rewarding future responses. In other words, VS is implicated in reward processing and motivation and DS is implicated in stimulus-response learning *and* decision-making.

1.4.3.4 SPEED Model

The formation of habits requires many trials, often several hundred or thousands of trials, compared to studies examining early learning. Additionally, the associations learned after so many trials are less reliant on feedback and are in fact, often resistant to changes in feedback (Balleine & O'Doherty, 2010). The subcortical pathways enable expertise development (SPEED) was postulated by the same group that hypothesized the COVIS model and thus many similarities are apparent (Ashby et al., 2007). SPEED relies on cortico-basal ganglia-thalamocortical circuits, as does COVIS, but SPEED focuses on posterior circuits that involve the body and tail of the dorsal caudate. SPEED postulates that the role of DS is to acquire stimulus-response associations and to train cortical-cortical connections between higher order sensory and pre-motor areas (Ashby et al., 2007; Helie et al., 2010; Soto et al., 2013). The theory maintains that the head of the caudate nucleus mediates early learning, and as the associations become more practiced progressing toward automaticity, more posterior regions of the striatum, namely the body and tail of the caudate nucleus, underlie late stage learning. Once automaticity has been achieved, involvement of dorsal caudate nucleus ceases, and stimulus-specific, automatic behaviours become mediated by cortical regions (i.e., pre-motor, motor and visual cortices; Ashby, et al., 2007).

Helie et al. (2010), cited as support for the SPEED model, investigated automatization of responses in a rule-based categorization learning paradigm that included over 10,000 trials, across 20 separate learning sessions, with fMRI data obtained in Sessions 1, 4, 10, and 20. They found that activity in DS was increased throughout Session 1, at the end of which

high levels of response accuracy were ultimately achieved (i.e., 89.6%). In subsequent sessions, DS activity was significantly attenuated (i.e., after Session 1) whereas cortical activation continued to correlate with accurate categorization even after extensive training.

1.4.4 Dorsal Striatum in Decision Making

Within the last 10-15 years, the claim that DS mediates decision making and response selection has gained traction with a large literature now bolstering this contention (Atallah et al., 2007; Nole M. Hiebert, Vo, et al., 2014; Brian Lau & Glimcher, 2007; B. Lau & Glimcher, 2008; Liljeholm & O'Doherty, 2012; A. A. MacDonald et al., 2014; P. A. MacDonald & Monchi, 2011; Smittenaar et al., 2012; Wunderlich, Dayan, & Dolan, 2012). Decision-making in this context is defined as the process of representing and assigning values to different response possibilities, then selecting and executing the most appropriate action (Rangel, Camerer, & Montague, 2008; Ryterska, Jahanshahi, & Osman, 2013). The claims regarding DS's role in learning versus decision making are inconsistent and their respective literatures have been developing independently from one another.

In examinations of DS in early learning, results often do not confer on this regions attributes that one would expect for a learning region. In naïve participants who are learning novel stimulus-response associations, learning regions are expected to be most active early on, when much of the learning is occurring (Nole M. Hiebert, Vo, et al., 2014), and to decrease their activity once the associations have been learned. The frequent finding that DS activity remains significantly increased above baseline after sequences (Reiss *et al.*, 2005), categorization rules (Helie *et al.*, 2010, Seger *et al.*, 2010), or stimulus-reward (Daw and Doya, 2006, Seger *et al.*, 2010), and response-reward (Delgado *et al.*, 2005, Ohira *et al.*, 2010) associations have been acquired should challenge the notion that DS underlies learning, yet has not instigated such a revision. The alternative interpretation that DS mediates response selection, which predictably improves once stimulus-response associations are learned, accounts for both the pattern of brain-behaviour relations and the observation that DS activity changes with exposure to learning events. Using single-cell recording in a go/no-go reversal learning paradigm in rats, Takahashi, Roesch, Stalnaker, and Schoenbaum (2007) found increased DS activity for rewarded odour cues only *after*

behavioural learning criteria were achieved. These findings support the view that DS mediates decision making, not learning *per se*.

Not only is there evidence that DS mediates decision making, but it seems to be specifically implicated in decision making that requires a degree of deliberation, before responses are enacted with little reflection or automatically (R. Cools & D'Esposito, 2011; Robertson et al., 2015). In fMRI studies, DS activity correlates with degree of uncertainty in category (Daniel et al., 2010), response-reward (Ohira et al., 2010), and stimulus-response decisions (Ali, Green, Kherif, Devlin, & Price, 2010; P. A. MacDonald et al., 2011). Further, investigations in patients with DS deficits reveal significant impairments for decisions requiring consideration and often *superior performance* relative to healthy controls for choosing *more* automatic responses (Ali et al., 2010; Coderre & van Heuven, 2013; Robertson et al., 2015).

1.4.5 DS mediates learning or decision making?

Decision-making and learning processes are often confounded in experimental designs looking at learning (Garrison et al., 2013; Jessup & O'Doherty, 2011). In stimulus-response learning experiments, for example, trials typically proceed as follows: a) a stimulus is presented and participants decide among a set of responses, and b) feedback regarding accuracy is provided, shaping stimulus-response associations. Learning is generally measured by the accuracy in selecting responses. Consequently, failing either to acquire stimulus-response associations or to select responses based on these learned associations could lead to impaired performance in these paradigms. In this way, learning and response selection are confounded. Further, in fMRI studies, a) deciding upon and enacting a response, and b) learning from feedback regarding response accuracy, are typically treated as a single event with all significantly-activated brain regions ascribed a role in learning *per se* (Dobryakova & Tricomi, 2013; Jessup & O'Doherty, 2011). For example, Delgado *et al.* (2005) examined learning to associate cards with concepts of 'high' versus 'low' via feedback. As is typical, they considered response selection (i.e., high vs. low decisions) and feedback portions of each trial (i.e., high vs. low feedback) as a single event. Compared to baseline, they found significant peaks in dorsal caudate

nucleus and VS, concluding that both regions mediate learning. Combining decision-making and feedback events caused ambiguity. Consequently, concluding that preferential DS activation was related to the response selection operation, whereas VS activity reflected learning through feedback is an alternative explanation for these data that is equally plausible.

Accordingly, some brain regions that might underlie decision processes guided by learned associations could erroneously be assigned a role in learning. Given that these processes are temporally intertwined and functionally interdependent, distinguishing them is very challenging, requiring novel experimental designs and nuanced interpretations. Learning and decision selection are entirely different processes phenomenologically, however, and distinguishing neural substrates of these different operations is important, with implications for understanding cognition in health and disease.

The small number of authors who also attempt to separate learning and decision-making find results that concur with this rationale. Wunderlich et al., 2012 provide a great example of a study that nicely distinguishes between learning and planning (a component of decision making), concluding that dorsal caudate is involved in planning whereas the posterior putamen (along the border between VS and DS) is recruited during habit learning. There are few papers that attempt to make this distinction between decision making and learning. In Liljeholm and O'Doherty (2012) and many of the studies outlined in Yin and Knowlton (2006), lesions in DS seem to impair different forms of learning, usually suggested from impaired performance on learning tasks involving selections. To perform these tasks correctly, the rodent must select the correct response using specific cues or feedback provided. Deficits in either selecting the response or learning from feedback will result in equally impaired performance on the task. What tends not to be discussed is the possibility that the DS lesions impair the ability to select the correct response even if the association might have been accurately learned. In an elegant study, Atallah et al., 2007 investigated the role of DS in learning versus selecting responses relying on learned associations. In a Y-maze task using odour cues, Atallah and colleagues observed impairment in rats' ability to consistently select a rewarded versus unrewarded arm for animals receiving infusions of inhibitory GABA agonist into DS compared to a saline solution during the learning phase

of the experiment. Initially, this seemed to suggest that animals receiving inhibitory infusions to DS were learning associations between odour cues and rewards more poorly. When both groups were later tested once the infusions were stopped, however, both experimental and control groups performed the selection task similarly. This demonstrated that associations were learned equally well for both experimental and control (i.e., saline-infused) groups during the learning session and suggested that inhibition of DS impaired the animal's ability to use learned associations to perform selections reliably. To complement this interesting finding, in another study, they found that GABA infusions to DS, at test phase, resulted in impaired selection performance compared to saline infusions to DS, although both groups had previously shown identical learning of these odour-reward associations during the training phase.

Taken together, these studies challenge the direct involvement of DS in learning and instead suggest a more specific role in performing selections based on previously-learned associations.

1.5 Ventral Striatum

1.5.1 Anatomy

VS is vascularized by the recurrent artery of Heubner, a branch of the anterior cerebral artery (Feekes & Cassell, 2006), and is composed of the NAcc and ventral portions of the caudate nucleus and putamen. As in DS, VS is populated by MSNs. However, MSNs in VS are smaller, and the dopaminergic input to VS is less dense compared to DS. Consequently, a dopamine pulse from VTA will stimulate VS more slowly, and with more variable intensity (Wickens et al., 2007). In an experiment by Zhang and colleagues (2009), neurons in rats were stimulated by nicotine, and firing frequency was monitored in both the dorsolateral striatum, and NAcc, homologous to DS and VS respectively in humans. In NAcc, dopamine responses to nicotine were graded and incremental, depending on the frequency and intensity of the stimulation. This is in stark contrast to the maximal (i.e., plateau) stimulation of DS in response to even the lowest frequency and intensity. In addition, VS stimulus durations are longer due to lower DAT concentration

(Wickens et al., 2007). These characteristics of VS suggest that it is adapted to a different function than DS, and perhaps that these attributes suit it to associating events or stimuli over time, for example in associative learning. The presence of specific glutamatergic connections aids in confirming this function. VS is connected, reciprocally, to the orbitofrontal, anterior cingulate, anterior temporal, as well as several limbic areas including the hippocampus, amygdala and hypothalamus (Kincaid, Zheng, & Wilson, 1998). These areas are heavily involved in encoding and associating salient environmental events as well as in motivating behaviour.

1.5.2 Function

VS is the downstream receiver of midbrain dopaminergic neurons from the VTA. Dopaminergic neurons in the midbrain are modulated by rewards and punishments (Redgrave & Gurney, 2006; Wolfram Schultz, 1998). Specifically, when a reward is received, a burst of dopamine is sent to VS, and when the organism receives punishing or negative feedback (i.e., no reward or lesser reward than was expected), dopamine tone is decreased in VS (Redgrave & Gurney, 2006; Wolfram Schultz, 1998). Therefore, the traditional role of the VS was to anticipate and respond to feedback via the midbrain dopamine signal (Ikemoto & Panksepp, 1999; B. Knutson, Fong, Adams, Varner, & Hommer, 2001). This was then expanded to include a role in reward learning (R. Cools, Clark, Owen, & Robbins, 2002; R. Cools, Lewis, Clark, Barker, & Robbins, 2007; Daw & Doya, 2006; Delgado et al., 2005; J. P. O'Doherty, 2004) and even general feedback-based learning in the absence of an overt reward (Atallah et al., 2007; Nole M. Hiebert, Vo, et al., 2014; Jessup & O'Doherty, 2011; P. A. MacDonald & Monchi, 2011)

A result often reported is that VS and DS are both ascribed a role in feedback-based learning. For example, in a recent meta-analysis of 35 fMRI studies of reinforcement learning through feedback—the majority of which confounded neural activity for response selection and feedback phases—found both VS and DS to be equally strongly associated with performing *feedback-based* learning. We argue that combining decision-making, and feedback events causes ambiguity. A plausible alternative explanation, consequently, is

that preferential DS activation could relate to the response selection operation, whereas VS activity reflected learning through feedback.

1.6 Striatum-mediated disorders

The striatum is central to many neurological and psychiatric disorders such as Parkinson's disease (Kish, Shannak, & Hornykiewicz, 1988), Huntington's disease (Bano, Zanetti, Mende, & Nicotera, 2011), addiction (Volkow, Wise, & Baler, 2017), bipolar disorder (Clark & Sahakian, 2008), schizophrenia (Barch & Ceaser, 2012), depression (Arnone, McIntosh, Ebmeier, Munafo, & Anderson, 2012), autism spectrum disorder (Park et al., 2017) and obsessive compulsive disorder (Jung et al., 2011), to name a few. Basic science research into the functions of the DS and VS is integral to understanding and developing effective treatments for striatum-mediated disorders. Two disorders, Parkinson's disease and obsessive compulsive disorder are discussed in depth below as these disorders will be central to later chapters.

1.6.1 Parkinson's disease

1.6.1.1 Pathophysiology

PD is a neurodegenerative disorder affecting 1% of the population over 60 years of age and 3% of the population over 80 in industrialized countries (Tanner & Goldman, 1996). It is mainly characterized by the motor symptoms of bradykinesia, or slow movement, rigidity, and tremor. The cardinal motor symptoms of this disorder are caused by the degeneration of dopamine-producing neurons in the SNc. This degeneration is caused by the accumulation of alpha-synuclein, a protein regularly found in healthy neurons that may function in neurotransmitter vesicle trafficking (Diao et al., 2013). It is thought that aggregation of alpha-synuclein negatively impacts other cell processes ultimately leading to programmed cell death (Dauer & Przedborski, 2003; Jellinger, 2012). When enough degeneration occurs in the SNc, delivery of dopamine to the DS, declines causing the balance between the direct and indirect pathways of the cortico-basal ganglia-thalamocortical motor circuit to increase signaling through the indirect pathway releasing DRD2, 3, 4 from dopaminergic inhibition, and decrease signaling through the direct

pathway (Wichmann, DeLong, Guridi, & Obeso, 2011). These changes result in increased activity in the internal segment of the globus pallidus, inhibiting the thalamus, and ultimately, regions of the motor cortex. When between 50-80% of the SNc dopaminergic neurons degenerate, the hypokinetic features seen in PD begin to emerge.

1.6.1.2 Treatment Strategies

At all stages of the disease, dopamine replacement is an effective treatment for improving motor symptoms. Dopamine replacement therapy can be prescribed in a variety of forms, namely dopamine precursors such as L-3,4-dihydroxyphenylalanine (L-dopa), or dopamine agonists. Dopamine precursors are often prescribed in conjunction with a dopamine decarboxylase inhibitor to prevent the conversion of L-dopa to active dopamine in the peripheral circulation, thereby increasing the availability of L-dopa within the brain. Dopamine precursors elevate dopamine levels in the brain, alleviating the motor symptoms associated with PD. Dopamine agonists are chemical substrates with a similar structure to dopamine, and can bind to and activate dopamine receptors directly.

1.6.1.3 Cognitive Deficits

Cognitive dysfunction is now an undisputed, non-motor symptom of PD that leads to significant impairment in quality of life (Barone et al., 2009; Schrag, Jahanshahi, & Quinn, 2000). In PD, some cognitive deficits relate to dopamine depletion in DS, and are remediated, at least partially, by dopaminergic therapy. Other cognitive deficits arise as a consequence of dopaminergic therapy. Increasingly, it is understood that impairment can occur due to overdose of brain regions that receive dopamine from VTA (see R. Cools, 2006; P. A. MacDonald & Monchi, 2011 for reviews). These regions include VS, prefrontal, and limbic cortices. Unlike SNc, the VTA is relatively spared throughout the course of PD, and as a result, regions innervated by VTA retain near-normal levels of dopamine (R. Cools, 2006). Therefore, it has been proposed that dopamine replacement therapy overdoses VTA-innervated regions, impairing functioning. As the disease progresses alpha-synuclein accumulates in cortical cells throughout the cortex leading to broader cognitive symptoms (Pereira et al., 2012). Finally, other transmitter systems

including acetylcholine and serotonin also deteriorate in patients with PD leading to cognitive dysfunction as well as mood and anxiety (Calabresi et al., 2006; Ray & Strafella, 2012; Scatton, Javoy-Agid, Rouquier, Dubois, & Agid, 1983).

The most common method in testing the effect of dopaminergic therapy on cognition is through the use of the exogenous dopamine withdrawal procedure. Patients are instructed to abstain from taking dopamine precursors for a minimum of 12 to a maximum of 18 hours, and dopamine agonists for a minimum of 16 to a maximum of 20 hours before testing begins, constituting the OFF state. Performance in this state is then compared to the ON state where the patient takes the medication as prescribed. Another method for investigating this effect involves comparing performance of medicated PD patients with patients who have never been medicated, or *de novo* PD patients. The advantage of the former method is that it removes the confounds related to receptor changes due to chronic dopaminergic therapy as well as disease progression. Severity can differ significantly across patients at the time of clinical diagnosis and as the disease progresses (Postuma et al., 2015). By comparing performance in ON and OFF states in a single patient, within-subject differences can be examined without the likelihood of comparing patients who have different disease durations.

1.6.1.4 Dopamine Overdose Hypothesis

The dopamine overdose hypothesis attempts to explain the cognitive impairments seen in PD as a function of varying concentrations of endogenous dopamine in different brain regions. Those that are dopamine depleted at baseline are improved; whereas, brain regions that are dopamine replete are impaired by dopaminergic therapy. DS is a brain region that is improved by dopamine replacement therapy; whereas, those mediated by a VTA-innervated regions are impaired.

Gotham, Brown, and Marsden (1988) were among the first to propose the overdose hypothesis. They investigated cognitive function in patients with PD both on and off dopaminergic medication using a series of tasks including the Paced Auditory Serial Addition Task, Wisconsin Card Sorting Task, Visual-visual Conditional Associative

Learning Test, Word Fluency Tasks, and Subject-ordered Pointing Task. A short description of each task is presented below.

- 1) The Paced Auditory Serial Addition Task is a measure of general attention, and working memory. Participants hear a series of numbers and are instructed to add the most recent number to the number that followed it in the series. For example, in the series *one, two, three*, the participant would be required to add the number *two* with *one*, resulting in *three* and then add the next number, *three*, to the previous numbers, resulting in *six*.
- 2) The Wisconsin Card Sorting Task is a measure of set-shifting, or the ability to flexibly update changing rules. Briefly, participants are told to match sample cards containing objects of various shapes, colours, and numbers to a probe card. They are not told on what dimension (i.e., colour, shape, or number) to match sample cards to the probe card, however, and need to determine this using a trial-and-error approach. The category matching rules change throughout the task.
- 3) The Visual-visual Conditional Associative Learning Test involves learning associations between arbitrary visual stimuli. Before the test, one of six cards with geometric designs is randomly paired to one of six colours. Participants are shown cards with geometric designs and are instructed to choose the colour that the card belongs to, and are given feedback. Through trial and error, participants learn to associate a particular colour to each geometrical design.
- 4) In the Word Fluency Tasks, participants are instructed to generate words based on a category cue, in a defined period of time (i.e., animals or boys names).
- 5) Finally, the Subject-ordered Pointing Task involves initiating a series of responses whilst monitoring their execution. Briefly, a series of stimuli are arranged on a sheet of paper. On several successive sheets of paper, the stimuli are presented in a different order. The participant is instructed to point to one stimulus per page, aiming to point to each different stimulus without pointing to the same one twice.

Stimuli include representational drawings, abstract images, and words that evoke a low amount of imagery.

All participants completed all of these measures and were tested both on and off dopamine replacement therapy. The delay between the two testing sessions was approximately one week. PD patients were randomly divided into two groups with order of testing counterbalanced across patients such that one group began the first testing session on dopaminergic medication, and the other first performed testing off medication. Each testing session involved a different version of the tasks listed above, and the order of the tasks was further counterbalanced with half of the participants beginning with one version, and the other half with the other version.

When tested in the OFF state, PD patients made more errors in the Wisconsin Card Sorting Task, and generated fewer words per category on the Word Fluency Tasks compared to their ON state. When tested on their medication, they performed more poorly on the Visual-visual Conditional Associative Learning Task, as well as the Subject-ordered Pointing Task. At its most basic level, the Wisconsin Card Sorting Task, and the Word Fluency Tasks are measures of decision-making, or response selection. Conversely, the Visual-visual Conditional Associative Learning Test and the Subject-ordered Pointing Task involve learning and working memory. Studies of decision-making and response selection have implicated DS, a result that is entirely in line with the results of Gotham and his colleagues. In addition, VS and the pre-frontal cortex, two regions that are innervated by VTA, have been shown to mediate association learning and working memory, respectively.

Since the overdose hypothesis was first proposed in 1988, few functional neuroimaging studies in PD have confirmed increased activity related to dopamine therapy in DS and/or in cortical regions reciprocally connected to DS. Even fewer studies demonstrate behavioural improvements *and* associated neural changes related to dopaminergic therapy in PD. Mattay et al. (2002) found that activations in motor regions during a simple motor response (i.e., supplementary motor area, cerebellum, lateral premotor, sensorimotor, and parietal cortical regions) were larger on compared to off dopaminergic therapy in PD

patients measured with fMRI. Keypress responses to single-digit stimuli were neither improved nor impaired by dopamine replacement in this study, however. Similarly, Feigin et al. (2003) found that *l*-dopa increased activation in premotor cortex, a region reciprocally connected to SNc-innervated DS, though motor learning performance was not altered. Finally, Fera et al. (2007) reported medication-induced behavioural *improvements* in interference in a modified, colour-word Stroop task involving key-presses. Stroop-related interference has been shown previously to be mediated by DS (Ali et al., 2010). Though neural activity in DS was not increased, it was in cortical regions reciprocally connected to DS (i.e., dorsal lateral prefrontal cortex, and parietal lobe) on compared to off medication corresponding to improved performance when print colour and colour word were incongruent.

Using functional neuroimaging, a small number of investigations support or at least partially bolster the dopamine overdose hypothesis (Argyelan et al., 2008; R. Cools et al., 2007; Feigin et al., 2003; Kwak, Müller, Bohnen, Dayalu, & Seidler, 2012; Van Eimeren et al., 2009). R. Cools et al. (2007) examined the effect of dopaminergic therapy on regional brain activity with fMRI in PD patients while they learned stimulus-reward associations and reversals through trial-and-error and probabilistic feedback. *l*-dopa attenuated regional brain activity in the VTA-innervated NAcc on the final error during stimulus-reward contingency reversals, just before patients began correctly responding to the updated stimulus-reward association. Arguably, this is the point at which patients learned the new stimulus-reward relationship, guiding correct responses on the subsequent trial. Despite fMRI signal differences, however, dopaminergic therapy did not correspondingly impair learning of the stimulus-reward contingency reversal. Argyelan et al. (2008) investigated the effect of dopaminergic therapy using positron emission tomography (PET) on default mode network (DMN). DMN normally deactivates during externally-oriented and goal-directed cognition (Di & Biswal, 2014). They found that parts of the DMN that are VTA-innervated—the ventromedial prefrontal cortex and insula—deactivated as expected during motor sequence learning in healthy controls and PD patients tested off dopaminergic therapy but not in PD patients following an *l*-dopa infusion. Though there were no corresponding ON-OFF performance differences, absence of deactivation could be interpreted as abnormal processing in VTA-innervated brain regions

in PD patients related to dopaminergic therapy. Van Eimeren et al. (2009) found that dopamine agonists and *l*-dopa reduced the reward prediction error-related neural response (i.e., the response related to the difference between expected and actual rewards received) in VS, whereas only dopamine agonists reduced the reward prediction error-related neural response in the VTA-innervated orbitofrontal cortex. These responses were not correlated with online behavioural changes, though the reward prediction error response in orbitofrontal cortex on dopamine agonists correlated with risk-taking behaviour in a task performed once patients were out of the scanner. Feigin et al. (2003) found that *l*-dopa reduced occipital association cortical activity measured with PET in PD patients during motor sequence learning. Trial-by-trial motor sequence learning efficiency and accuracy was not worsened by an *l*-dopa infusion, though PD patients had less accurate explicit report of final motor sequences suggesting some learning impairment. Finally, Kwak et al. (2012) found that *l*-dopa reduced fMRI activation in ventral putamen in PD patients while they explicitly learned motor sequences *and* this reduction in neural signal correlated with decreased early phase learning. This study directly supported the dopamine overdose hypothesis.

At odds with the prefrontal, peri-cingulate, anterior cingulate, and parietal cortical regions dopamine overdose hypothesis, Mattay et al. (2002) used fMRI to investigate the effect of *l*-dopa on working memory. In an *n*-back task, PD patients indicated when the current stimulus matched the stimulus from *n* trials earlier. Similar cortical regions were engaged during this task in PD patients in the ON and OFF states, though activations of VTA-innervated brain regions were larger in the OFF condition, consistent with notions of dopamine overdose. However, greater ON-OFF differences in fMRI activations correlated with *poorer* accuracy in the OFF relative to ON states. These findings were most easily interpreted as *poorer* working memory performance related to *less efficient* function of VTA-innervated brain regions in the OFF state. Van Eimeren et al. (2009) found that dopamine agonists *increased* feedback-related activation in orbitofrontal cortex in PD relative to testing on *l*-dopa or off dopaminergic therapy. This activation in orbitofrontal cortex correlated positively with a measure of risk-taking. Finally, Shiner et al. (2012) investigated the effect of dopaminergic therapy in PD patients on a) stimulus-reward discrimination learning through probabilistic feedback in the Learning Session and

subsequently on b) selecting the most probabilistically-rewarded stimuli in the Performance Session. In the Performance Session, a) all pairs from the Learning session and b) novel pairs formed by coupling the most-rewarded and least-rewarded stimuli and all stimuli with which they had not previously been paired during the Learning session were tested. Contrary to previous findings, (Ghilardi et al., 2007; A. A. MacDonald et al., 2014; Seo, Beigi, Jahanshahi, & Averbeck, 2010; Vo et al., 2014), and there were no ON-OFF fMRI signal differences (R. Cools et al., 2007) dopaminergic therapy had no detrimental effect on efficiency or accuracy of stimulus-reward association learning. In the Performance Session, greater accuracy in choosing the most probabilistically rewarded stimuli was achieved in the ON relative to OFF state for newly-created stimulus pairs only, when greater integration of information was required, though no ON-OFF fMRI signal differences were noted. The dopamine overdose hypothesis was not supported and though dopaminergic therapy improved response selections that have previously been shown to be DS-mediated (Grahn et al., 2008; Nole M. Hiebert, Vo, et al., 2014), corresponding neural signal changes did not occur in this study.

PD and dopaminergic therapy are expected to *simultaneously* have *opposing* effects on neural activation in, and functions associated with, SNc- versus VTA-innervated brain regions. Recognizing an evidence gap, Aarts et al. (2014) aimed to critically test this concept using a rewarded task-switching paradigm. Task-switching refers to the ability to shift strategies, adapting to changing situational demands (R. Cools, Barker, Sahakian, & Robbins, 2001). It has been shown to depend upon the SNc-supplied DS (R. Cools et al., 2001; Robertson et al., 2015). Reward processing and anticipation of reward have been shown to engage VTA-innervated VS and orbitofrontal cortex (B. Knutson & Cooper, 2005). Aarts et al. (2014) investigated the effect of a) cued-switching between responding to simultaneously-appearing word stimuli (i.e., left or right) and arrows (i.e., pointing left or right), and b) reward anticipation. As predicted, PD patients' abilities to switch between responding to simultaneously appearing word or arrow stimuli, based on a preceding cue, was improved in the ON state. This correlated with greater DS blood-oxygenation level dependent (BOLD) signal on relative to off dopaminergic therapy. In contrast, anticipating a high versus low reward, based on a cue that preceded each trial, had no effect on accuracy or response time (RT) though previous research has shown that higher relative to lower

anticipated rewards results in greater errors and longer RTs, a so-called *reward cost* (Aarts et al., 2010). Further, dopaminergic therapy had no effect on behaviour based on reward anticipation. Despite no behavioural differences, signal in the VTA-innervated VS ROI was *lower* on relative to off dopaminergic therapy during reward anticipation. Investigating individual differences through correlational analyses, PD patients with *greater* ON relative to OFF VS region of interest (ROI) activation evidenced greater ON more than OFF *reward costs* (i.e., poorer behaviour). That is, medication-induced *increases* in VS ROI activation correlated with *poorer* performance, not fully consistent with the dopamine overdose hypothesis.

Especially in early PD, a) endogenous dopamine levels in SNc- versus VTA-innervated brain regions, and b) replenishing versus overdosing effects of exogenous dopamine in these brain regions respectively, are proposed to be important determinants of the cognitive profile (R. Cools, 2006; P. A. MacDonald & Monchi, 2011). This framework is prevalent and effectively accounts for behavioural patterns across numerous PD studies (R. Cools, 2006; Dirnberger & Jahanshahi, 2013; Vaillancourt, Schonfeld, Kwak, Bohnen, & Seidler, 2013). Studies that fully support these concepts are lacking, however. In fact, demonstrations of simultaneous but opposite effects of dopaminergic therapy on both behavioural and neural measures of SNc- versus VTA-innervated brain regions to this point are not found in the literature. Previous studies included only small numbers of PD patients, in some cases ten or fewer (Feigin et al., 2003; Mattay et al., 2002; Van Eimeren et al., 2009), possibly contributing to the lack of strong support to date. In some cases, the behavioural measures potentially resulted from combined operations ascribed to both SNc-innervated brain regions (e.g., response selection, retrieval processes) and VTA-supplied areas (e.g., stimulus-response learning) accounting for patterns that were not straightforward (Feigin et al., 2003; Mattay et al., 2002; Shiner et al., 2012).

1.6.2 Obsessive compulsive Disorder

1.6.2.1 Pathophysiology

Obsessive compulsive disorder (OCD) is a psychiatric disorder prevalent in 1.2% of adults and is described by the National Institute of Mental Health as typically chronic with a gradual onset (Bokor & Anderson, 2014). OCD is characterized by two major symptoms: obsessions and compulsions (Bokor & Anderson, 2014). The former is defined as disturbing thoughts, urges, or impulses, such as thoughts of harm and death of a loved one, fears of contamination, persistent doubting, counting and the need for symmetry (Bokor & Anderson, 2014; Chamberlain, Blackwell, Fineberg, Robbins, & Sahakian, 2005). Compulsions are repetitive behaviours or mental acts that individuals affected by the disorder feel driven to perform, including repeatedly checking locks and appliances, excessive hand-washing, and organizing objects symmetrically (Bokor & Anderson, 2014; Chamberlain et al., 2005).

The disorder exhibits diversity in severity, however, the symptoms tend to follow a general pattern: obsessive thoughts, anxiety, compulsions, and temporary relief (Bokor & Anderson, 2014). For example, with respect to sanitization, patients may have an irrational fear of being contaminated by germs, resulting in illness or death. Anxiety often ensues and patients feel driven to carry out certain tasks to reduce their distress. The individual may wash or clean repetitively until a “feeling” of cleanliness is achieved, whereas a typical individual may wash until observing that they are clean. Completion of the respective compulsions result in temporary relief and the cycle repeats. Patients spend a substantial amount of time with their obsessions and carrying out compulsions, and this can be costly to maintaining jobs and relationships. Anxiety is at the core of OCD and the disorder was in fact classified as an anxiety disorder in the Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV). In the current iteration, DSM-V, OCD is now classified as a separate disorder.

Recently, OCD has been linked to deficits in the striatum using evidence from structural and functional MRI. Structural MRI studies utilizing voxel-based morphometry have

consistently found volumetric differences within the striatum with the consensus being reduced volume of DS (Piras et al., 2015; Riffkin et al., 2005) and increased volume of VS (Piras et al., 2015; Pujol, Soriano-Mas, Alonso, & et al., 2004; Yoo et al., 2008; Zarei et al., 2011). The volumetric abnormalities in OCD are also reflected in resting state basal activity. PET and resting fMRI have found increased glucose metabolism and increased activity in regions of VS compared to controls (Baxter et al., 1987; de Vries et al., 2017; Del Casale et al., 2011; Gursel, Avram, Sorg, Brandl, & Koch, 2018; Le Jeune et al., 2010; Perani et al., 1995; Rauch, 1997). Conversely, resting state activity in DS is reduced compared to controls (Del Casale et al., 2011; Rubin, Villanueva-Meyer, Ananth, Trajmar, & Mena, 1992). Interestingly, activation in VS increased compared to rest in response to symptom-provoking stimuli (Figeet et al., 2011; Mataix-Cols et al., 2004; Rauch, Jenike, Alpert, & et al., 1994). Mataix-Cols et al. (2004) categorized OCD patients based on their subtype, either contamination, checking, or hoarding subtype, and conducted a block design symptom-provocation task where patients with OCD and healthy controls viewed blocks of images pertaining to each of those subtypes as well as neutral images. Interestingly, different OCD-subtypes evidenced dissimilar brain activity patterns in the striatum. Contamination-subtype patients had higher activity in ventral caudate nucleus compared to controls, whereas ventral putamen was increased compared to control in patients with the checking-subtype. Hoarding-subtype did not result in changes in the striatum. This study supported the notion that OCD is a multifaceted psychiatric disorder that may involve different brain regions depending on subtype. Taking everything together, OCD patients seem to have increased volume and baseline activity in VS, and diminished volume and activity in DS.

1.6.2.2 Treatment Strategies

The first line pharmacological therapy for the treatment of OCD, as it is for anxiety disorders and depression, is selective serotonin reuptake inhibitors (SSRIs), which inhibit serotonin transporters (SERT or 5-HTT) impairing the removal of serotonin from synapses and prolonging their effects (Chamberlain et al., 2005; Hirschtritt, Bloch, & Mathews, 2017; Seibell & Hollander, 2014). Unfortunately, between 40-60% of patients do not respond to SSRI treatment suggesting that augmenting serotonin may not be addressing the

underlying pathology and instead masking it by reducing the anxiety associated with the disorder (Atmaca, 2016; Chamberlain et al., 2005; Seibell & Hollander, 2014). SSRIs are typically used as adjunct therapy with cognitive behavioural therapy (CBT) focusing on exposure and response prevention (ERP; Chamberlain et al., 2005; Hirschtritt et al., 2017; Seibell & Hollander, 2014). Patients with OCD undergoing ERP first create a hierarchy of triggers related to their symptoms. For example, if a patient suffered from the contamination-subtype of OCD, he or she may rank using a public water fountain as less anxiety-provoking than touching a public bathroom doorknob. Patients then carry out controlled exposures, working up their hierarchy. An example of an exposure from the instances above would be using a public water fountain until the level of anxiety diminishes significantly. Using ERP in conjunction with developing strategies to understand and resist compulsions typically constitutes the psychological therapy component (Hirschtritt et al., 2017; O'Neill & Feusner, 2015). Even with CBT and pharmacological intervention, between 30-40% of patients do not respond to treatment (Atmaca, 2016), stimulating research into non-serotonergic medications and other treatment options.

1.6.2.3 Cognitive Deficits

Structural and functional changes in patients with OCD could be linked to cognitive dysfunction related to OCD symptomatology. Deficits in VS and DS could lead to dysfunction in reward processing, error detection, decision making, and cognitive flexibility.

VS has been implicated in reward processing (Ikemoto & Panksepp, 1999; W. Schultz et al., 1992) stimulus-response learning through feedback (Nole M. Hiebert, Seergobin, Vo, Ganjavi, & MacDonald, 2014; Nole M. Hiebert, Vo, et al., 2014; Vo et al., 2014), and reversal learning (i.e., behavioural adaptations in response to changing stimulus-reward contingencies; R. Cools et al., 2002; R. Cools et al., 2007; Remijnse, Nielen, van Balkom, & et al., 2006; Swainson et al., 2000). It appears that reversal learning (Remijnse et al., 2006) and reward learning (Nielen, den Boer, & Smid, 2009) are diminished in OCD patients, coupled with decreased VS activity compared to healthy controls. Remijnse et al. (2006), ascribe striatal deficiencies that contribute to impairments in task-switching and

reversal learning to be the neurological foundations of cognitive inflexibility and ineffective behavioural adaptation to changing stimuli in OCD patients, which manifest as compulsive behaviours. As discussed above, obsessive-compulsive behaviours have been linked to hyperactivity in the reward-processing circuitry, as evidenced by augmented striatal metabolism in OCD patients at rest and in response to symptom-provoking stimuli (Baxter et al., 1987; de Vries et al., 2017; Del Casale et al., 2011; Figeo et al., 2011; Gursel et al., 2018; Le Jeune et al., 2010; Perani et al., 1995; Rauch, 1997). Figeo et al. (2011), contend that this hyperactivity of the VS occurs by surrendering the regular responsiveness of VS to natural rewards (e.g., food, water, sex). Augmented baseline VS activity in patients with OCD hinders performance on VS-mediated tasks and may play an integral role in OCD symptomatology.

As discussed above, DS has been reported to mediate cognitive flexibility (P. A. MacDonald & Monchi, 2011), selective attention (A. A. MacDonald et al., 2014), and decision making (Atallah et al., 2007; N. M. Hiebert, Owen, Seergobin, & MacDonald, 2017; Robertson et al., 2015). OCD patients have shown impaired executive functions in tasks examining cognitive flexibility (Del Casale et al., 2011; Vriend et al., 2013), and response inhibition (Del Casale et al., 2011; van Velzen, Vriend, de Wit, & van den Heuvel, 2014). As cognitive flexibility and response inhibition appear to be impaired in OCD patients, this may be linked to the inability to choose naturally rewarding behaviours over compulsive actions (Vriend et al., 2013). Nakao et al. (2005) conducted a colour-word Stroop task, where colour words (i.e., Red, Blue, Green), are presented in font colours that are either congruent with the colour word (i.e., Red, Blue, Green), or incongruent with the colour word (i.e., Red, Blue, Green). Patients with OCD and healthy controls were instructed to name the colour of the font, rather than read the colour word while brain activity was simultaneously recorded using fMRI. Patients with OCD took longer to complete the Stroop task and did not exhibit significant activity in DS, as did the healthy controls. In this task, the role of DS has been shown to mediate inhibiting the response that is more salient (i.e., colour word) and outputting the visual, font colour information (Ali et al., 2010; Coderre & van Heuven, 2013; Djamshidian, O'Sullivan, Lees, & Averbeck, 2011; Fera et al., 2007; Larson, Clayson, Primosch, Leyton, & Steffensen, 2015; C. M. MacLeod, 1991; C. M. MacLeod & MacDonald, 2000; Nakao et al., 2005; Wright

& Wanley, 2003). Impaired cognitive flexibility and response inhibition could be related to deficits in OCD which in turn might lead to compulsive actions.

A present model of OCD based on data discussed above suggests that obsessions and compulsive behaviours may be linked to a disproportion between hyperactivity in the VS and hypoactivity in the DS while processing incoming information. Dysfunctional reward circuitry centred in the VS is expected to result in an ability to respond to natural rewards and instead is modulated by stressful, obsession-related stimuli (Baxter et al., 1987; de Vries et al., 2017; Del Casale et al., 2011; Figeo et al., 2011; Gursel et al., 2018; Le Jeune et al., 2010; Perani et al., 1995; Rauch, 1997). Hypoactivity in DS producing deficits in cognitive flexibility and response inhibition might produce difficulty switching away from thinking of obsessions, and performing adaptive actions over maladaptive compulsions (Del Casale et al., 2011; van Velzen et al., 2014; Vriend et al., 2013).

1.7 Functional Magnetic Resonance Imaging

MRI is a non-invasive technique that allows for the visualization of brain structures using a large electromagnet and radio waves. While in the magnet, all water molecules inside the tissues become aligned. During data collection, radio waves are introduced causing the water molecules to increase in energy and spin away from this alignment. After the radio wave is stopped, these molecules release this energy and relax back to alignment. The rate at which these molecules relax depends on many factors including tissue type. What MRI measures is the different relaxation times allowing for the visualization of different tissues within the brain. Generally, the larger the electromagnet, the higher spatial resolution of the images. At 3T, the spatial resolution of the images ranges from 1-3mm in most studies. In higher field strength, such as 7T, the resolution increases to around 500µm (Glover, 2011). Functional MRI uses an electromagnet to visualize differences in oxygenated and deoxygenated blood, referred to as BOLD in the brain. This BOLD response in different brain regions can be correlated with various functions relative to rest or other control functions. The theory behind fMRI is that areas of the brain that recruit more oxygenated blood, stored as oxyhemoglobin, are more active than areas that do not. All processes involved in neural signaling from action potential propagation, neurotransmitter vesicle

binding to the synaptic junction, and release and reuptake of neurotransmitters, require energy in the form of adenosine triphosphate (Glover, 2011). To utilize this energy effectively requires oxygen absorbed from the bloodstream. Oxygen uptake by neurons results in an increased local concentration of deoxyhemoglobin and waste products resulting in vasodilation and increased blood flow containing oxygenated blood (Glover, 2011). This process is called the hemodynamic response and is what is most often modelled in fMRI experiments. Changes in blood oxygenation and blood flow, referred to as Blood-Oxygenation Level Dependent responses, are visualized and measured in fMRI. Specifically, it is the difference in magnetic characteristics between deoxygenated and oxygenated blood that allow for visualization. Deoxyhemoglobin is highly paramagnetic compared to oxyhemoglobin and this paramagnetism creates magnetic fields that change the relaxation rates of the water molecules that can be visualized (Glover, 2011). An important feature of fMRI is temporal resolution which refers to ability to measure changes in BOLD over time. Action potentials are very fast, on the order of milliseconds, whereas the hemodynamic response function is sluggish, peaking approximately 5 seconds after the neural stimulus, and returning to resting levels after 8-16 seconds (Glover, 2011). By taking great consideration when stimuli or responses occur, and using sophisticated analysis methods, clearer pictures of BOLD activity can be obtained and correlated with neural responses (Glover, 2011).

While in the fMRI scanner, subjects complete tasks, or just simply rest, and active brain areas can be visualized during these processes. Using healthy participants, fMRI-generated BOLD responses can suggest brain regions that are preferentially correlated with certain functions. Once the cognitive functions have been mapped in healthy individuals using fMRI, testing functions of interest in patient populations that have demonstrated impairment in the target brain regions can better assess whether these regions are critical for the function under investigation.

1.8 Stimulus-response Learning

Stimulus-response learning, discussed in sections 1.4 and 1.5, has been an area of intense research for a multitude of reasons. (1) Stimulus-response learning forms the basis for how

organisms interact and thrive in their environments due to its role in adaptive behaviour (Thorndike, 1898), (2) stimulus-response learning is easily tested with tasks adaptable for non-human primate and rodent animal models as well as for humans, and (3) stimulus-response learning is mediated by the striatum, a region implicated in many disorders. Many models of reinforcement learning and instrumental conditioning, have been created using stimulus-response tasks. Here, we adapt a stimulus-response learning and decision-making task to address the controversy regarding DS's role in learning versus decision-making (Chapter 2). Additionally, we implement this task in patients with striatum-mediated disorders, namely Parkinson's disease (Chapter 3), and obsessive compulsive disorder (Chapter 4) to investigate the neural mechanisms of cognitive deficits and symptoms in these disorders. Our stimulus-response learning task was designed to individually investigate, and tease apart, decision making and learning, as well as to identify the brain regions that mediate them. Briefly, participants learned to associate abstract images with button-presses while brain activity was recorded in 3T fMRI. We modeled a) the phase during which participants decided amongst options and selected responses, separately from b) the stage when participants learned about associations through feedback regarding the accuracy of their choices (Figure 1.3; Nole M. Hiebert, Vo, et al., 2014). In some experiments, we further tested participants' ability to select and enact responses that they learned during the first phase of the study, investigating the brain regions that mediated these decisions.

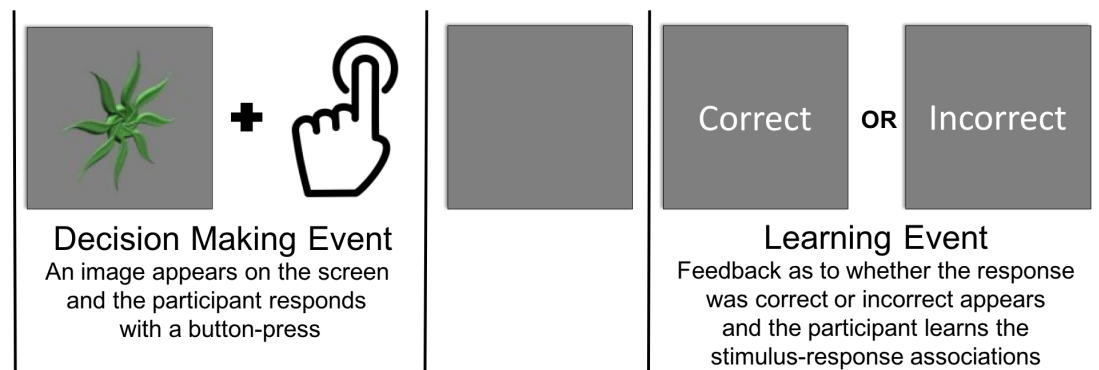


Figure 1.3 Schematic of the stimulus-response task used

The stimulus-response task used in Nole M. Hiebert, Vo, et al. (2014), as well as in Chapters 2-4. The task was designed to allow for separate investigation of decision making and learning. In each trial there is a Decision Making Event and a Learning Event. In the Decision Making Event, an abstract image appears on the screen and the participant chooses a response out of multiple response options. After the response is made, the Learning Event occurs, during which participants receive and process feedback as to whether their response was correct or incorrect. Participants use this feedback to learn image-button press pairings (i.e., stimulus-response associations).

Using this task in healthy, young adults (Nole M. Hiebert, Vo, et al., 2014), we found activation in DS only during the Decision Making Event, not during learning through feedback (i.e., the Learning Event). Further, DS activity during the decision stage of our trials only occurred for trials occurring later in the learning session, when the slope of learning was shallower, as participants were already selecting responses guided by associations that they had acquired in earlier trials. In contrast, activity in VS correlated with the Feedback Event of our stimulus-response learning trials as has been shown by others (R. Cools et al., 2007; W. Schultz et al., 1992). Further, feedback-related VS activation was greatest in the earliest phase of learning when the slope of behavioural change was steepest, indicative of greatest stimulus-response association learning.

In addition to the fMRI experiment in healthy adults described above (Nole M. Hiebert, Vo, et al., 2014), we have previously tested behaviour only in patients with PD on and off dopaminergic therapy completing a similar task (Nole M. Hiebert, Seergobin, et al., 2014; Vo et al., 2014). Learning stimulus-response associations in patients with PD was comparable to controls at baseline and impaired with dopaminergic therapy. This pattern suggests that learning stimulus-response associations is not mediated by the dopamine-deficient DS in PD but rather a VTA-innervated brain region.

All results support the original investigation in that DS does not mediate stimulus-response learning. Given the robustness and replicability of the results, this task was chosen to investigate the role of DS in patients with PD on and off dopaminergic therapy (Chapter 2), in patients with OCD (Chapter 3) and DS in habit learning (Chapter 4). Combining fMRI with our stimulus-response task on and off dopaminergic therapy in PD, as well as in patients with OCD provides an extremely powerful paradigm for testing the neural substrates of learning and decision making. Nole M. Hiebert, Vo, et al. (2014) provided

fMRI data that was correlational making it impossible to definitively state the necessity of brain regions for various functions. Conversely, in our behavioural studies investigating stimulus-response learning in patients with PD on and off dopaminergic medication, allow us only to speculate regarding the brain regions mediating these functions using behavioural and pharmacological effects. Testing patients with PD on and off dopaminergic therapy while measuring brain activity using fMRI allows us to make causal inferences rather than just correlational. To reiterate, in unmedicated PD patients, DS functions and neural activity are depressed, whereas VS operations and activation levels are spared. Dopaminergic therapy remediates DS dopamine depletion and improves function (R. Cools, 2006; P. A. MacDonald et al., 2011). Additionally, exogenous dopamine distributes non-selectively, increasing dopamine even to the relatively-replete VS. As a consequence, dopaminergic medications have been shown to attenuate neural activity and worsen functions performed by VTA-innervated brain regions, presumably due to *dopamine overdose* (R. Cools, 2006). In this way, comparing the OFF and ON states, *a double dissociation* in terms of behaviour and neural activity is observed comparing DS and VS. In OCD, we will test for the first time both learning and decision making in the same patients within the same scanning session to truly understand deficits in OCD. Finally, we will modify this task by pre-training participants on stimulus-response association learning to investigate DS's role in late-stage learning to the point of automaticity.

1.9 Hypotheses

We hypothesize that DS does not mediate stimulus-response learning—either goal-directed or habit learning—but rather underlies selections among response options, referred to as decision making. VS, on the other hand, mediates feedback-based stimulus-response learning but only in the early stages. In three experiments, DS and VS will be probed using similar stimulus-response paradigms in patients with PD on and off dopaminergic therapy, in patients with OCD, and in healthy, young controls testing later-staged stimulus-response learning.

Chapter 2 explored the role of DS and VS in goal-directed, stimulus-response learning in patients with PD tested on and off dopaminergic medication. To review, functions mediated by DS have been shown consistently to be impaired off dopamine replacement therapy, and improved with medication. However, functions mediated by VTA-innervated regions, such as VS, are expected to be impaired on medication due to dopamine *overdose*, and normal off medication. Much of the data supporting this hypothesis is behavioural only with speculation that these are the brain regions that are affected by dopamine. We have a task that contrasts, in contiguous experimental conditions, functions of DS and of VTA-innervated brain regions. Contrasting PD patients on and off dopamine replacement therapy, while brain activity is estimated with fMRI, we predict a double dissociation of function that can be related to neural activity in different brain regions because we are pairing tests of PD patients off and on dopaminergic therapy with fMRI. This method allows us to directly test whether behavioural effects arise because of changes in activity in brain regions that differ in their dopaminergic innervation depending on whether the patient is off or on dopaminergic therapy. For example, this will allow us to fully refute DS's role in learning if we see dopaminergic therapy worsens learning efficiency but simultaneously increases DS activation in fMRI. In contrast we expect that when learning slope declines, VS activity will parallel this. These predicted double dissociations in terms of behaviour and brain function would be compelling evidence that DS is a decision making brain region rather than a region that mediates learning. Further, this paradigm allows for fully testing the dopamine overdose hypothesis. The effect of exogenous dopamine on VTA-innervated regions will be directly investigated. We hypothesized that decision making would be impaired and correspondingly activity in DS would be diminished at baseline and improved with dopaminergic medication in PD patients. In contrast, we predict that stimulus-response learning and activity in VS will be near-normal at baseline and impaired with dopaminergic therapy. In this way, we are using PD as a model to answer basic science questions about the neural substrates of cognitive functions. With this approach, we can separately investigate the role of DS and VS in decision making and stimulus-response learning by modulating the level of dopamine in the brain regions that we expect to mediate these separate functions, *causing* changes in the functioning and fMRI signal in these regions. Understanding DS- and VS-mediated cognitive functions

additionally informs cognitive symptoms present in patients with PD, and has implications for treatment. Currently, dopaminergic therapy is titrated to relieve DS-mediated motor symptoms, without taking into account the potential overdose of VTA-innervated regions. Ultimately, this greater understanding will prompt clinicians to formulate medication strategies that consider both motor and cognitive symptoms, as well as individual patient needs. This further provides a critical test for the prevalent dopamine overdose hypothesis discussed in section 1.6.1.4.

Chapter 3 investigated the cognition related to changes in DS and VS activation in patients with OCD using a similar version of the stimulus-response learning task previously applied in healthy young controls (Hiebert et al., 2014) and in PD patients (Chapter 2 of this current thesis). Though the literature focusing specifically on the separate functions of VS and DS in OCD is relatively sparse, there is some evidence that in OCD VS is hyperactive and DS is hypoactive at baseline. During striatal-mediated tasks however, DS and VS are both impaired, with respect to behaviour and activity (Remijnse et al., 2006; Vriend et al., 2013). We speculate that these baseline levels of VS and DS activity adversely impact VS- and DS-mediated cognitive functions, such as reward learning (Remijnse et al., 2006) and cognitive flexibility (Vriend et al., 2013), respectively. We hypothesize that OCD patients will exhibit stimulus-response learning and decision making impairments and that these effects will correlate with VS and DS task-related activation respectively. The stimulus-response task allows for simultaneous investigation of DS and VS function within-subject. Within-subject, and within the same testing session is essential in patient populations like PD and OCD, where severity of symptoms and medication levels can fluctuate from day to day, and even during different time points throughout the day that can impact behavioural performance and brain activity compared to healthy controls. Using our paradigm removes these confounds. The overarching aim of this study was to further our investigations of DS- and VS-mediated cognitive functions and to better understand how various disease states impact them. Further, this research has the potential to clarify the cognitive deficits that arise in OCD and how they might be better treated, based on an improved understanding of their neural basis.

Chapter 4 investigated the role of DS in late-stage, stimulus-response, so-called habit learning in the animal literature. Young, healthy participants learned to associate abstract images with right or left button presses explicitly before strengthening these associations through stimulus-response trials with (Session 1) and without (Session 2) feedback. In Session 1, trials were divided into response-selection and feedback events to separately assess decision versus learning processes. In Session 2, trials consisted only of response-selection with no feedback. Session 3 evaluated the degree to which stimulus-response associations had achieved automaticity using a location Stroop task. We hypothesized that DS-dependent decision making occurs specifically when deliberation is required. We hypothesized that DS would only be recruited when associations still required some consideration before responding. Critically, we expected that DS activation would cease before stimulus-response automaticity arose, which would refute the role of DS in this process. The overarching aim of this investigation was to address the controversy that DS mediates late-stage stimulus-response automaticity versus decision making.

1.10 Objectives

The objectives of the studies were to:

1. Delineate the function of DS and VS in early goal-directed, and late stimulus-response association learning
2. Determine how dopaminergic therapy affects behavioural performance and brain activity in stimulus-response learning and decision making in PD.
3. Directly test the dopamine overdose hypothesis within-subject, assessing different brain regions at the same time, within the same task.
4. Investigate how different patterns of DS and VS activity in OCD relate to decision making and stimulus-response learning functions, as well as how they might mediate different symptoms of this disorder.

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Chapter 2

2 Dorsal striatum does not mediate feedback-based, stimulus-response learning

Learning associations between stimuli and responses is essential to everyday life. Dorsal striatum (DS) has long been implicated in stimulus-response learning, though recent results challenge this contention. We have proposed that discrepant findings arise because stimulus-response learning methodology generally confounds learning and response selection processes. In 19 patients with Parkinson's disease (PD) and 18 age-matched controls, we found that dopaminergic therapy (DA) *decreased* the efficiency of stimulus-response learning, with corresponding *attenuation* of ventral striatum (VS) activation. In contrast, DA *improved* response accuracy related to *enhanced* DS BOLD signal. Contrasts *between* PD patient and control groups fully support these within-subject patterns. These double dissociations in terms of behaviour and neural activity related to VS and DS in response to DA, strongly refute the view that DS mediates stimulus-response learning through feedback. Our findings integrate with a growing literature favouring a role for DS in decision making rather than learning, and unite two literatures that have been evolving independently.

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2.1 Introduction

The view that the dorsal striatum (DS)—consisting of the bulk of the caudate nucleus and putamen—is critical for stimulus-response learning, is well-entrenched (Brovelli, Nazarian, Meunier, & Boussaoud, 2011; Chiu, Jiang, & Egner, 2017; Thompson RL, 1963; Yin & Knowlton, 2006). Despite the prevalence of this view, learning is often preserved in patients (Exner, Koschack, & Irle, 2002; Nole M. Hiebert, Seergobin, Vo, Ganjavi, & MacDonald, 2014; A. A. MacDonald et al., 2013; Vo et al., 2014) and animals (Atallah, Lopez-Paniagua, Rudy, & O'Reilly, 2007) with DS dysfunction.

Potentially underlying the discrepancies in the stimulus-response learning literature, response selection decisions and learning are often intrinsically confounded (Jessup & O'Doherty, 2011; McDonald & Hong, 2004). In stimulus-response learning experiments, trials generally proceed as follows: a) a stimulus is presented and participants perform a response, and b) feedback regarding response accuracy is provided. Feedback is the means through which stimulus-response associations are learned. Accuracy in selecting a learned response provides the learning measure. Performance depends upon both decision and learning processes. Failing either to acquire stimulus-response relations or to correctly select learned responses produces impaired performance. Further, in fMRI studies, a) deciding upon and enacting a response, and b) learning from feedback, are typically treated as a single event with all significantly activated brain regions ascribed a role in learning *per se* (Jessup & O'Doherty, 2011; Poldrack, Prabhakaran, Seger, & Gabrieli, 1999). Accordingly, some brain regions that might underlie response selection could erroneously be assigned a role in learning. The objective of the current study was to directly test this confound in patients with PD, using a stimulus-response learning paradigm previously shown to separate decisions and learning, producing differential patterns of activity in DS and VS (Nole M. Hiebert, Vo, et al., 2014).

Combining fMRI with behavioural manipulations in patients with PD tested both off and on dopaminergic therapy, provides a powerful approach for investigating striatum-mediated cognitive functions. In PD, the quintessential motor symptoms arise when dopamine-producing neurons in the substantia nigra pars compacta (SNc) degenerate to

seriously restrict dopamine supply to the DS (Kish, Shannak, & Hornykiewicz, 1988). In contrast, dopamine-producing neurons in the adjacent ventral tegmental area (VTA) are relatively spared in PD, especially in the early disease stages, resulting in adequate endogenous dopamine to regions such as VS, composed of the nucleus accumbens and ventral portions of the caudate and putamen (Kish et al., 1988). Consequently, in unmedicated PD patients, DS functions and neural activity are depressed, whereas VS operations and activation levels are spared.

Dopaminergic therapy remediates DS dopamine depletion and improves function (Cools, 2006; P. A. MacDonald et al., 2011). Unfortunately, exogenous dopamine distributes non-selectively, increasing dopamine even to the relatively-replete VS. As a consequence, dopaminergic medications have been shown to attenuate neural activity and worsen functions performed by VTA-innervated brain regions, presumably due to *dopamine overdose* (Cools, 2006). In this way, comparing the OFF and ON states, *a double dissociation* in terms of behaviour and neural activity is observed comparing DS and VS.

If DS mediates stimulus-response learning, it is predicted that a) DS activity will correlate with learning measures and with the moment when stimulus-response association learning occurs (i.e., the Feedback Event, when outcome information regarding response accuracy is provided) and b) learning efficiency and DS signal will improve with dopaminergic therapy in PD. These outcomes are predicted because the DS is significantly dopamine depleted and its functions are impaired at baseline in PD. DS functions and activity *improve* with dopamine replacement (P. A. MacDonald & Monchi, 2011).

In contrast, if DS mediates stimulus-response decision performance and VS mediates stimulus-response association learning, as we expect, a) DS activity will correlate with accuracy of decision performance and with the moment when response selection occurs (i.e., the Stimulus-Response Decision Event), and b) accuracy of stimulus-specific decisions and DS signal will *improve* with dopaminergic therapy in PD. Further, we predict that a) VS activity will correlate with learning measures and with the moment of learning during the Feedback Event, and b) efficiency of learning and VS signal will *decrease* with dopaminergic therapy in PD. These predictions are based on the knowledge

that DS functions and activation improve with dopaminergic therapy in PD, whereas functions and activation of VTA-innervated brain areas are attenuated by exogenous dopamine in PD, which overdoses these relatively dopamine-replete regions.

2.2 Materials and methods

2.2.1 Participants

Twenty-three participants with PD and 19 age- and education-matched healthy controls participated in this experiment. All participants with PD were previously diagnosed by a licenced neurologist, had no co-existing diagnosis of dementia or another neurological or psychiatric disease, and met the core assessment for surgical interventional therapy and the UK Brain Bank criteria for the diagnosis of idiopathic PD (Hughes, Daniel, Kilford, & Lees, 1992). All PD and no control participants were treated with dopaminergic therapy. Age- and education-matched controls were within five years of age (average difference was 3.6 years) and five years of education (average difference was 2.4 years) to the matched PD patient. Participants with PD were recruited through the movement disorders database at the London Health Sciences Centre. Participants abusing alcohol, prescription or illicit drugs, or taking cognitive-enhancing medications including donepezil, galantamine, rivastigmine, memantine, or methylphenidate were excluded from participating. Additionally, participants obtaining a Montreal Cognitive Assessment (MoCA) score of 24 or less were excluded.

The motor sub-scale of the Unified Parkinson's Disease Rating Scale (UPDRS) was scored by a licenced neurologist with sub-specialty training in movement disorders (P.A.M.) to assess the presence and severity of motor symptoms for all patients both off and on dopaminergic medication. Control participants were also screened to rule out undiagnosed neurological illness. Mean group demographic, as well as cognitive and affective screening scores for all patients and controls in each experimental group were recorded (Table 1). UPDRS motor subscale scores off and on dopaminergic therapy, daily doses of dopamine replacement therapy in terms of ι -dopa equivalents (LED), and mean duration of PD was also recorded (Table 1). Calculation of daily LED for each patient was based on the theoretical equivalence to ι -dopa(mg) as follows: ι -dopa dose(mg) \times 1 + ι -dopa controlled release(mg) \times 0.75 + ι -dopa(mg) \times 0.33 if on entacapone(mg) + amantadine(mg) \times 0.5 + bromocriptine(mg) \times 10 + cabergoline(mg) \times 50 + pergolide(mg) \times 100 + pramipexole(mg) \times 67 + rasagiline(mg) \times 100 + ropinirole(mg) \times 16.67 + selegiline(mg) \times 10 (Wullner et al., 2010).

All participants provided informed written consent to the protocol before beginning the experiment according to the Declaration of Helsinki. This study was approved by the Health Sciences Research Ethics Board of the University of Western Ontario.

2.2.2 Experimental design

Participants with PD were randomly divided into two groups and all participated in two sessions on separate days. Different stimulus-response pairs were used in Sessions 1 and 2. Both Sessions 1 and 2 were separated into two phases. Phase 1, the learning phase, constituted the phase during which stimulus-response associations were learned through feedback. Phase 2, the performance phase, comprised the phase during which stimulus-specific responses learned in Phase 1 were performed without further feedback. Participants with PD randomly assigned to Group 1 (OFF-ON) performed Session 1 off dopaminergic therapy and Session 2 on dopaminergic therapy. In contrast, PD patients randomized to Group 2 (ON-OFF) performed Session 1 in the ON dopaminergic therapy state and Session 2 in the OFF state. Although control participants did not take dopaminergic therapy in either session, their data were analyzed to correspond to the ON-OFF order of the PD patient to whom they were matched. Matching was performed prior to data analysis at the time of data collection. This controlled for possible order, fatigue, and practice effects. Participants with PD took their dopamine medication as prescribed by their treating neurologist during ON testing sessions, but abstained from taking *all* dopaminergic medication including dopamine precursors such as L-dopa, aromatic-L-amino-acid decarboxylase inhibitors such as carbidopa, and catechol-O-methyltransferase (COMT) inhibitors such as entacapone (Comtan) for a minimum of 12 to a maximum of 18 hours, and dopamine agonists, such as pramipexole (Mirapex), ropinirole (Requip), or pergolide (Permax), as well as amantadine (Symmetrel), rasagiline (Azilect), and selegiline (Eldepryl or Deprenyl) for 16 to 20 hours before beginning OFF testing sessions. All patients confirmed that they complied with these medication instructions. Ten PD patients and eight controls were in the OFF-ON group, whereas nine PD and ten controls were in the ON-OFF group.

In Phase 1, the learning phase of each session, participants learned to associate abstract images with one of three button-press responses. Images were computer-generated with *GroBoto* (Braid Art Labs, Colorado Springs, USA). In each trial, an abstract image appeared in the centre of a projection screen until the participant responded with a button-press. Feedback (i.e., ‘Correct’ or ‘Incorrect’) was provided after every response and in this way, participants learned to associate each of the abstract images with the appropriate button-press response through trial and error. Trials were organized into blocks. After each block, participants were provided with a percentage score, summarizing their learning performance. Participants completed a maximum of 12 blocks. Once participants scored greater than 75% on two successive blocks, Phase 1 ended. Our aim was to examine early learning. Further, we wanted to avoid accuracy reaching ceiling so that we could also investigate, as a separate measure, decision performance. If after 12 blocks the participant was not responding at an accuracy level greater than chance (~33%), his/her data were not included in the analysis for either the OFF or ON Sessions. Before proceeding to Phase 1, participants received 20 practice trials with different images from those employed during the main experimental sessions to become familiar with the procedure. In Phase 2, the performance phase of each session, stimuli presented in Phase 1 were shown again. Participants were asked to provide the stimulus-specific button-press responses that they had learned in Phase 1. No feedback was provided to preclude new feedback-based learning during this phase that was aimed to test selection of accurate responses. Again, different sets of images were used in Session 1 and Session 2.

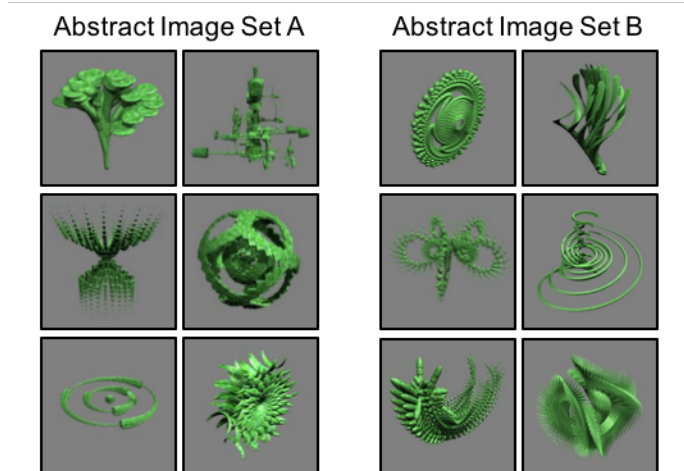


Figure 2.1 Abstract images presented in Phase 1 and Phase 2.

Abstract Image Set A and Set B refer to the images presented in Session 1 and Session 2 respectively. Images were associated with a button pressed by the index, middle, or ring finger buttons.

Both Phases 1 and 2 of Sessions 1 and 2 were performed while fMRI measures were simultaneously recorded. Twelve abstract images were used in the experiment, six during each session of testing (Figure 2.1). There were 24 trials per block in Phase 1 of each session, with each abstract image occurring four times in random order per block. Two images were assigned to each the second, third, and fourth button on the button box per session and participants pressed these buttons with their index, middle, and ring fingers, respectively. A button-press response was required to advance from the feedback phase to the next trial. In this way, in each trial, motor responses were included in both Stimulus-Response Decision and Feedback Events (Figure 2.2A).

Trials in the Learning Phases proceeded as follows: (i) a cross appeared in the centre of the projection screen for 500 ms; (ii) a blank screen occurred for 500 ms; (iii) an abstract image was presented until a button-press response was performed (i.e., the Stimulus-Response Decision Event); (iv) a blank screen appeared for a variable amount of time sampled from an exponential distribution (mean: 2500 ms; minimum: 525 ms; maximum: 7000 ms); (v) feedback (i.e., “Correct” or “Incorrect”) appeared for 1000 ms followed by a green circle that appeared in the centre of the projection screen signifying to the participant to press the

first button with his/her thumb to advance to the next trial (i.e., the Feedback Event); (vi) a blank screen appeared for a variable amount of time sampled from an exponential distribution (mean: 2500 ms; minimum: 525 ms; maximum: 7000 ms).

A distractor task lasting approximately 15 minutes (data not shown) was employed between the Phases 1 and 2 in both Sessions 1 and 2. This was to prevent rehearsal of stimulus-response associations as well as to make stimulus-response decisions more challenging. In Phase 2 of each session, participants performed three blocks of 24 trials, in which the same six images studied during Phase 1 were presented in random order, four times per block. Participants provided the button-press response that they had learned for each image during Phase 1. No feedback regarding accuracy was provided in Phase 2 of each session, precluding further feedback-based learning. Parameters for each trial in Phase 2 were otherwise identical to those in Phase 1 with the exception that the Feedback Event was omitted. Figures 2.2A and B present example trials in Phases 1 and 2.

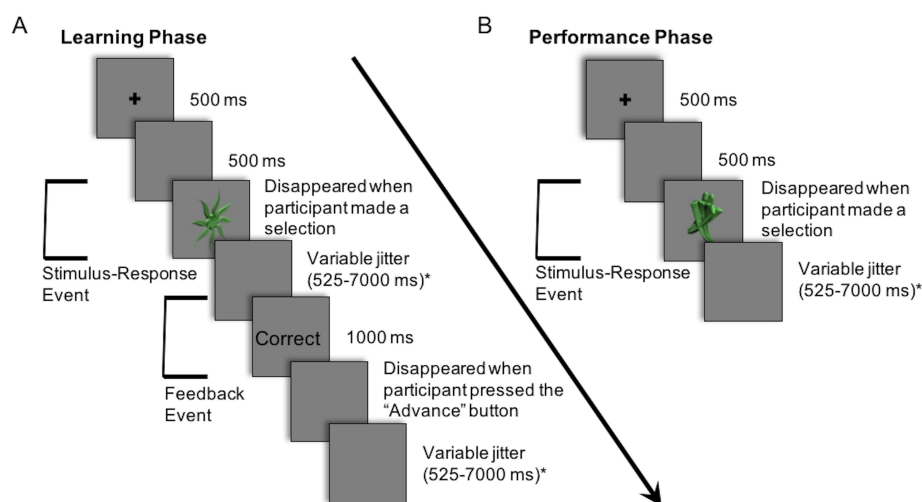


Figure 2.2 Example of a single trial in Phase 1 and Phase 2.

A) Participants learned to associate six abstract images with one of three button-press responses in Phase 1. The following is an example of a trial: (i) a cross appeared in the centre of the projection screen for 500 ms; (ii) a blank screen occurred for 500 ms; (iii) an abstract image was presented in the centre of the projection screen until a button-press response; (iv) a blank screen appeared for a variable period of time sampled from an exponential distribution (mean: 2500 ms; minimum: 525 ms; maximum: 7000 ms); (v) feedback (i.e., 'Correct' or 'Incorrect') appeared for 1000 ms; (vi) a blank screen appeared for a variable period of time

sampled from an exponential distribution (mean: 2500 ms; minimum: 525 ms; maximum: 7000 ms). **B)** Participants recalled the responses to the learned images in the absence of feedback in Phase 2. Trials in Phase 2 were identical to the Phase 1 except that feedback was omitted. * The inter-stimulus and inter-trial intervals (ISI and ITI, respectively) were jittered between the response and feedback and between the offset of feedback and the beginning of the subsequent trial to create two fMRI events within each trial: a) the Stimulus-Response Decision Event and b) the Feedback Event for Phase 1. In Phase 2, the ITIs were jittered between the response and the subsequent trial, as the Feedback Event was omitted.

2.2.3 Statistical analysis

2.2.3.1 Behavioural

Executing stimulus-specific response selections in Phase 2 depended on how well these associations were learned during Phase 1 in each session. We hypothesized that PD and medication would affect learning. We therefore implemented measures to better isolate decision performance. First, we aimed to equate the degree to which stimulus-response associations were acquired across participants and sessions by imposing a learning criterion in Phase 1. That is, once participants reached a learning criterion of 75% correct on two consecutive blocks or once they completed 12 blocks, Phase 1 ended. Second, we used an Adjusted-Savings Score to evaluate accuracy of stimulus-specific response selections during Phase 2. This score was calculated as follows for each session: % accuracy of Block 1 of Phase 2 \div % accuracy of Last Block of Phase 1. By weighting response-selection performance relative to previous learning performance in Phase 1, we corrected for learning differences between participants and across sessions. This score permitted evaluation of stimulus-specific response selection performance independent of medication effects on stimulus-response learning.

Efficiency of encoding stimulus-response associations across the Phase 1 of each session was estimated by the rate of change of correct responses across the session. The slope of change was measured by summing the scores obtained at the end of each block over the total number of blocks required to reach the pre-set learning criterion (i.e., standard slope of the linear regression function, Microsoft Excel, 2011), as follows:

$$b = \frac{\sum (x - \bar{x})(y - \bar{y})}{\sum (x - \bar{x})^2}$$

where b is the slope, and x and y are the sample means of the number of blocks and block scores, respectively.

For each of our dependent measures, Adjusted-Savings Score and slope, 2×2 mixed ANOVAs with Group (PD versus control) and Medication (ON versus OFF) as the between-subject, and within-subject variables, respectively. Simple effects will be investigated in the case of significant interactions. Simple effects tests will include:

- Within-subject
 - PD OFF versus PD ON
 - control OFF versus control ON
- Between-subject
 - OFF PD versus control
 - ON PD versus control

2.2.3.2 Imaging acquisition

During data collection of this experiment, the MRI scanner at Robarts Research Institute at the University of Western Ontario was upgraded. fMRI data were collected either in a 3 Tesla Siemens Magnetom Trio (before upgrade) or Magnetom Prisma (after upgrade) with Total Imaging Matrix. Nine PD patients and seven control participants were scanned on the Magnetom Trio. The scanning parameters for each scanner before and after the upgrade were identical. We obtained a scout image for positioning the participant and T_1 for anatomical localization. Number of runs of T_2^* -weighted functional acquisitions varied depending on the participant's rate of learning but ranged from a minimum of one to a maximum of four runs. Each run was of variable length and therefore consisted of a variable number of blocks of 24 trials. A distractor task lasting approximately 15 minutes was administered between Phases 1 and 2 in both sessions. All participants performed

Phase 2 as the final fMRI run. All runs lasted on average eight minutes with one whole brain image consisting of 43, 2.5mm-thick slices taken every 2.5s. The field of view was oriented along the anterior and posterior commissure with a matrix of 88×88 pixels, an isotropic voxel size of $2.5 \times 2.5 \times 2.5 \text{ mm}^3$. The echo time was 30ms and the flip angle was 90° .

2.2.3.3 FMRI data analysis

Statistical Parametric Mapping Version 8 (SPM8; Wellcome Department of Imaging Neuroscience, London, United Kingdom) was used in conjunction with Matrix Laboratory (MATLAB; MathWorks, Inc., Natick, Massachusetts, United States) to complete fMRI analysis. Images were slice-time corrected, reoriented for participant motion, spatially normalized to the standard Montreal Neurological Institute (MNI) template, smoothed with an 8mm full-width half-maximum Gaussian kernel, and high-pass filtered (0.0056Hz).

Individual participant data were modeled using fixed effects analysis using SPM8. Regressors were formed using onsets and durations of psychological events of interest, particularly Stimulus-Response Decision, Feedback, and post-feedback Rest Events, with the canonical hemodynamic response function. The inter-stimulus interval between Stimulus-Response Decision and Feedback Events was not explicitly modelled to minimize over fitting the data. If the randomly generated inter-trial interval (ITI) between the Feedback Event and the Stimulus-Response Decision Event for the next trial was between 525-2000ms, the final 500ms of this interval was modeled to form the Rest Event. If the ITI was between 2000-4000ms, the final 1000ms comprised the Rest Event for that trial. Finally, for ITIs that were greater than 4000ms, the final 2000ms were included as the Rest measure. The aims were to a) separate the Stimulus-Response Decision, Feedback, and Rest Events as much as possible, and b) create Rest events with variable durations to match the Stimulus-Response Decision and Feedback Events. Stimulus-Response Decision Events were defined as the time from the onset of the abstract image until the participant made a button-press response. The Feedback Event was defined as the time from the onset of feedback (“Correct” or “Incorrect”) until and including the button-press response that participants made when the green circle appeared on the projection

screen, signalling their readiness to proceed to the next trial. This ended the Feedback Event. In this way, a motor response occurred during the Stimulus-Response Decision and Feedback Events.

A single General Linear Model (GLM) was created for Phase 1 in each session to investigate regional BOLD responses for Stimulus-Response Decision, Feedback, and Rest Events. Number of predictor functions corresponded to the number of blocks completed by each participant multiplied by the three event types (i.e., Stimulus-Response Decision, Feedback, and Rest). A similar GLM was created for Phase 2 in each session to investigate regional BOLD responses for Stimulus-Response Decision and Rest Events, with regressors corresponding to each of the three blocks completed in each of the sessions, multiplied by the two event types (i.e., Stimulus-Response and Rest). Contrasts were made at the individual level for each session comparing Stimulus-Response Decision, Feedback, and Rest Events for Phase 1, and Stimulus-Response Decision and Rest Events for Phase 2. Correct and incorrect trials were examined separately. At the group level, two GLMs were created, one for Phase 1 and the other for Phase 2. The Phase 1 GLM consisted of separate regressors for correct and incorrect Stimulus-Response Decision minus Rest, and Feedback minus Rest Events for both PD and control, off and on medication, yielding 16 regressors. Age and Order were also added as covariates. Similarly, the Phase 2 model contained 8 regressors, separated into correct and incorrect Stimulus-Response Decision minus Rest Events for both PD and control participants, off and on medication.

First, group-level contrasts examined events **collapsed across Group (PD and control) and Medication (OFF and ON) to confirm that we replicated the results from Hiebert et al., (2014b)**. The contrasts of interest for Phases 1 and 2 were as follows: (i) Stimulus-Response Decision Events minus Rest in Phase 1, (ii) Stimulus-Response Decision minus Feedback Events in Phase 1, (iii) Stimulus-Response Decision Events minus Rest in Phase 2, (iv) Feedback Events minus Rest in Phase 1, (v) Feedback Events minus Stimulus-Response Decision Events in Phase 1, (vi) correct versus incorrect Feedback Events in Phase 1. Peaks in these contrasts are reported at a significance level of $q < 0.05$ corrected for multiple comparisons using false discovery rate (FDR) at the voxel level, unless otherwise noted.

We next conducted Bayesian analysis, because critical conclusions regarding DS's role in stimulus-response learning depend on accepting null effects. Specifically, refuting the entrenched view that DS mediates stimulus-response learning is accomplished by showing that a) DS activation *does not* arise during the Feedback Event when stimulus-response associations are learned. There is a justified bias against publishing negative findings, in that with frequentist approaches, the probabilities of Type II (i.e., falsely failing to reject the null hypothesis) and Type I errors (i.e., falsely rejecting the null hypothesis) are asymmetric. Type I errors are set at a clear maximum, usually less than 0.05, whereas Type II errors vary across studies in terms of magnitude and determinants (Dienes, 2014) not pre-determined by the experimenter. Bayesian analysis allows directly contrasting the probability of the null and the alternative hypotheses in a symmetrical way, putting these hypotheses on an equal footing, and directly comparing the relative fit of the two models (Dienes, 2014). Bayesian analyses were therefore performed to investigate the strength of null effects that arose. Additionally, the strength of significant effects was investigated by conducting Bayesian analyses on the strength of DS and VS activity during Stimulus-Response Decision and Feedback events, respectively. Bayes' factor one-sample *t*-tests were conducted separately for PD patients and control participants, using average beta values extracted from left and right anatomical DS and VS ROIs during Stimulus-Response Decision and Feedback Events in the following contrasts:

- i. Stimulus-Response Decision Events across Phase 1 collapsed across Medication session (OFF and ON)
- ii. Stimulus-Response Decision Events across Phase 2 collapsed across Medication session (OFF and ON)
- iii. Correct minus Incorrect Feedback events across Phase 1 collapsed across Medication session (OFF and ON)

ROIs were created using the Automated anatomical labeling atlas (Tzourio-Mazoyer et al., 2002), and WFU PickAtlas (Maldjian, Laurienti, Kraft, & Burdette, 2003) in conjunction with MarsBaR (Brett, Anton, Valabregue, & Poline, 2002). The left and right DS ROI included left and right dorsal caudate nucleus and left and right dorsal putamen at a level of $z > 2$ mm in MNI space. The left and right VS ROIs were similarly created and included

the left and right ventral caudate nucleus and putamen at a level of $z \leq 2$ mm in MNI space, as well as the NAcc.

Using the Bayes' factor of three as the cut-off, previously indicated to be the Bayesian corollary of $p < 0.05$ in frequentist hypothesis testing (Dienes, 2014), we tested whether the extracted beta values were indeed zero. If the Bayes' factor of the average beta value is less than three, it strongly supports the null hypothesis, that the activation level is not greater than zero.

Next, we investigated **brain-behaviour correlations to confirm that behavioural performance was related to DS versus VS activity patterns**. We tested whether BOLD signal in striatal regions correlated with behavioural indices of response selection decisions and learning respectively. Specifically, we tested whether activity in two DS versus two VS ROIs taken from Hiebert et al., (2014b), correlated with the Adjusted-Savings Score (i.e., our measure of response-selection decisions), and with Learning Slope (i.e., our measure of learning efficiency). Correlations were performed separately for PD and healthy control groups in the event that learning and response selection performance differed across groups collapsed across medication session. The two right and left DS and two right and left VS ROIs from Hiebert et al., (2014b) were employed for the correlation analysis in the present study using the MarsBar Toolbox in SPM8 (Brett et al., 2002). DS ROIs were centered on the dorsal head of the caudate nucleus ($x=\pm 18$, $y=24$, $z=6$), and dorsal putamen ($x=\pm 29$, $y=9$, $z=6$). For VS, $x=\pm 10$, $y=8$, $z=-4$, and $x=\pm 12$, $y=18$, $z=-6$, centering on the nucleus accumbens and ventral caudate nucleus respectively were used. Spherical ROIs centred on the aforementioned coordinates were created with a radius of 6mm. Beta values in our ROIs were extracted from four contrasts of interest: (i) Stimulus-Response Decision Events across Phase 2 for patients with PD across Sessions 1 and 2 (i.e., off and on dopaminergic medication); (ii) Feedback Events across Phase 1 for patients with PD across Sessions 1 and 2 (i.e., off and on medication); (iii) Stimulus-Response Decision Events across Phase 2 for healthy controls across Sessions 1 and 2; and (iv) Feedback Events across Phase 1 for healthy controls across Sessions 1 and 2. These average beta values for each ROI were correlated with behavioural measures of stimulus-specific

response selection (i.e., the adjusted savings scores) and learning (i.e., slope values) for each group separately.

Subsequently, **events of interest were examined for PD and Healthy controls separately comparing OFF and ON Medication sessions directly.** These within-subject contrasts of interest for Phases 1 and 2 were as follows: (i) PD OFF versus ON Stimulus-Response Decision Events in Phase 1; (ii) PD OFF versus ON Stimulus-Response Decision Events in Phase 2, (iii) PD OFF versus ON medication for Feedback Events in Phase 1; (iv) PD OFF correct minus incorrect Feedback Events versus ON correct minus incorrect Feedback Events; (v) control OFF versus ON Stimulus-Response Decision Events in Phase 1; (vi) control OFF versus ON Stimulus-Response Decision Events in Phase 2, (vii) control OFF versus ON medication for Feedback Events in Phase 1; (viii) and control OFF correct minus incorrect Feedback Events versus ON correct minus incorrect Feedback Events. For OFF-ON contrasts in PD patients and controls, peaks within the striatum were considered predicted and are reported at a significance level of $p \leq 0.001$, uncorrected for multiple comparisons. Peaks outside of the striatum are reported at a threshold of $q < 0.05$ FDR corrected at the voxel level. Striatal regions were defined using the Harvard-Oxford Subcortical Atlas in the FMRIB Software Library version 5.0 (FSL v5.0; Analysis Group, FMRIB, Oxford, United Kingdom). DS and VS are not distinct anatomical structures, which creates difficulty when attempting to separate them in an fMRI context. In a review, Postuma and Dagher (2006) define VS as $z \leq 2$, which we employed. Here, DS refers to portions of the caudate nucleus and putamen at a level of $z > 2$ mm in MNI space. VS was defined as the nucleus accumbens, caudate, and putamen at a level of $z \leq 2$ mm in MNI space. All cortical regions were defined using the Harvard-Oxford Cortical Atlas in the FMRIB Software Library version 5.0 (FSL v5.0; Analysis Group, FMRIB, Oxford, United Kingdom). All x, y, z coordinates are reported in MNI space.

Next, to clarify our within-subject contrasts that explored the effects of dopaminergic therapy on DS and VS function in PD patients, we **contrasted Group (PD versus control) in each of the Medication states separately.** The contrasts of interest for Phases 1 and 2 were as follows: (i) Stimulus-Response Decision Events minus Rest in Phase 1, (ii) Stimulus-Response Decision minus Feedback Events in Phase 1, (iii) Stimulus-Response

Decision Events minus Rest in Phase 2, (iv) Feedback Events minus Rest in Phase 1, (v) Feedback Events minus Stimulus-Response Decision Events in Phase 1, (vi) correct versus incorrect Feedback Events in Phase 1. For OFF-ON contrasts in PD patients and controls, peaks within the striatum were considered predicted and are reported at a significance level of $p \leq 0.001$, uncorrected for multiple comparisons. Peaks outside of the striatum are reported at a threshold of $q < 0.05$ FDR corrected at the voxel level.

2.3 Results

2.3.1 Behavioural data

Demographic, affective, and clinical data are presented in Table 2.1 and behavioural data for Phases 1 and 2 are presented in Table 2.2.

2.3.1.1 Demographic, affective, and clinical data

Three patients with PD were excluded because they obtained a Montreal Cognitive Assessment (MoCA) score of 24 or less, and a further one PD patient and one control participant failed to show any evidence of learning in Phase 1 in either Session 1 or 2 (explained below) and were therefore excluded from all analyses. Nineteen patients with PD and 18 age- and education-matched healthy controls were therefore included in the final analyses.

There were no significant demographic differences between PD and control participants (Table 2.1). Participants with PD scored significantly higher on both Beck Depression Inventory II and Beck Anxiety Inventory compared to controls regardless of medication status as is expected based on previous research. No differences were found in terms of depressive or anxiety symptoms between participants with PD measured off or on their dopaminergic medication. UPDRS scores were significantly higher in participants with PD measured off relative to on dopaminergic medication ($t > 6.00$, $p < 0.0001$), signifying greater PD signs when patients were in the unmedicated state.

Table 2.1 Demographic, clinical, screening cognitive, and affective measures for PD patients and healthy controls.

Group	<i>N</i>	Age	Edu	Duration	l-dopa (mg)	DA (<i>n</i>)	UPDRS OFF	UPDRS ON
PD	19	65.73 (1.80)	15.21 (0.69)	3.95 (0.60)	599.50 (46.37)	9	15.26 (1.48)	12.16 (1.32)
CTRL	18	65.06 (1.70)	15.00 (0.59)	-	-	-	-	-
Group	ANART	MOCA	BDI-II OFF	BDI-II ON	BAI OFF	BAI ON	Apathy OFF	Apathy ON
PD	124.80 (1.63)	27.05 (0.52)	8.31 (1.21)	7.94 (1.23)	7.57 (1.42)	6.47 (1.30)	10.05 (1.06)	10.68 (1.13)
CTRL	124.45 (1.51)	27.00 (0.28)	3.53 (0.56)	3.53 (0.70)	2.41 (0.58)	2.05 (0.55)	9.88 (0.79)	10.29 (0.95)

Values are presented as group means and standard error of the mean (SEM) in braces. Screening cognitive and affective measures were completed on medication unless otherwise stated. Dopaminergic therapy was not administered to control (CTRL) participants at any time during the experiment. Their data are presented here in the ON-OFF order corresponding to their matched PD patient. Edu – Years of education; Duration – Number of years since PD diagnosis; l-dopa (mg) - l-dopa equivalent dose in mg; DA – number of PD patients on dopamine agonists; UPDRS OFF – Unified Parkinson's disease rating scale motor score off medication; UPDRS ON – Unified Parkinson's disease rating scale motor score on medication; ANART – National Adult Reading Test IQ Estimation; MOCA – Montreal Cognitive Assessment total score out of 30; BDI-II OFF – Beck Depression Inventory II score measured when patients with PD were off medication and for CTRL participants during the off session of their corresponding PD patient; BDI-II ON – Beck Depression Inventory II score measured when patients with PD were on medication and for CTRL participants during the ON Session of their corresponding PD patient; BAI OFF – Beck Anxiety Inventory score measured when patients with PD were off medication and for CTRL participants during the OFF Session of their corresponding PD patient; BAI ON – Beck Anxiety Inventory score measured when patients with PD were on medication and for CTRL participants during the ON Session of their corresponding PD patient; Apathy OFF – Starkstein Apathy Scale score measured when patients with PD were off medication and for CTRL participants during the OFF Session of their corresponding PD patient; Apathy ON – Starkstein Apathy Scale score measured when patients with PD were on medication and for CTRL participants during the ON Session of their corresponding PD patient.

2.3.1.2 Response selection decision behavioural measure

Accuracy of selecting previously-learned stimulus-specific responses was measured using an Adjusted-Savings Score. The score obtained in Block 1 of Phase 2 was weighted relative to the final accuracy obtained during the last block of Phase 1 for each session. A 2×2 mixed ANOVA of the Adjusted-Savings Scores was conducted with Group (PD versus

control) as between-subject factor and Medication Session (OFF versus ON) as the within-subject variable. There were no significant main effects of Group ($F < 1$) or Medication ($F_{1,32} = 1.327$, $MSE = 235.00$, $p = 0.258$). The Group \times Medication interaction trended toward significance, $F_{1,32} = 4.007$, $MSE = 235.00$, $p = 0.054$, and was further investigated using pairwise comparisons. This revealed a *significantly improved* Adjusted-Savings Score for participants with PD tested ON compared to OFF dopaminergic medication ($t = 2.24$, $p = 0.038$; Figure 2.3A) as would be predicted if DS mediates decisions or response selections. There were no significant differences between OFF and ON sessions for control participants ($t = 0.70$, $p = 0.494$). Recall that control participants did not actually receive dopaminergic therapy but their data were analyzed to correspond to the ON-OFF order of the PD patient to whom they were matched. Additionally, there were no significant differences between PD and control groups for either the OFF ($t = 1.26$, $p = 0.104$) or ON ($t = 0.50$, $p = 0.308$) contrast.

Table 2.2 Behavioural measures for participants with PD and control participants.

Group	Adjusted-Savings Score (%)	Learning Slope
PD		
OFF	94.00 (3.70)	0.206 (0.023)
ON	104.75 (3.65)	0.165 (0.021)
Control		
OFF	102.86 (3.80)	0.186 (0.025)
ON	99.33 (3.75)	0.205 (0.23)

Values presented are mean (SEM). To reiterate, Adjusted-Savings Score was measured using the following equation: percent accuracy in Block 1 of Phase 2 \div percent accuracy in the last block of Phase 1. Slope was calculated using the block accuracy scores over the number of blocks in early and late halves using the slope of the linear regression function (Microsoft Excel 2011). All values are presented separately for PD patients in the OFF and ON medication sessions, and control participants in the sessions corresponding to the OFF and ON sessions for the PD patient to whom they were matched. Healthy controls did not receive dopaminergic therapy at any point in this study.

2.3.1.3 Stimulus-response association learning measure

Efficiency of stimulus-response association learning was estimated using the slope of accuracy change over the total number of blocks required to reach the learning criterion in Phase 1 (i.e., 75% accuracy on two consecutive blocks). Slope was calculated using the

linear regression function in Microsoft Excel (2011). A 2×2 mixed ANOVA on the slopes of learning obtained during Phase 1 was conducted with Group (PD versus control) as the between-subject factor and Medication Session (OFF versus ON) as the within-subject variable. There were no main effects of Group ($F<1$) or Medication ($F<1$). However, the Group×Medication interaction was significant, $F_{1,35}=4.46$, $MSE=0.004$, $p=0.042$. Investigated further using pairwise comparisons, we found significantly *slower* learning ON relative to OFF medication for PD patients ($t=2.17$, $p=0.044$; Figure 2.3B) but no medication difference for control participants ($t=0.92$, $p=0.368$), replicating what we found previously in patients with PD (Nole M. Hiebert, Seergobin, et al., 2014; Vo et al., 2014) and supporting the dopamine overdose hypothesis. Additionally, there were no significant slope differences between PD and control groups for either the OFF ($t=-0.17$, $p=0.568$) or ON ($t=0.85$, $p=0.200$) contrast.

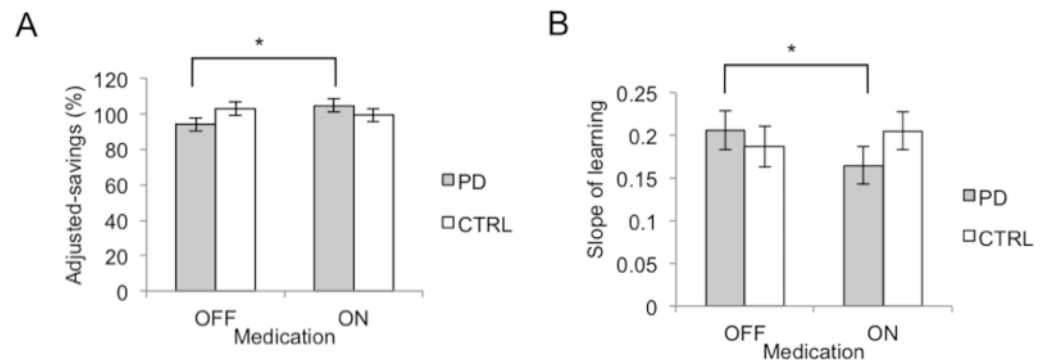


Figure 2.3 Effect of PD and dopaminergic therapy on learning and response selection.

A) Effect of PD and dopaminergic therapy on Adjusted-Savings Score. Adjusted-Savings Score served as a measurement of stimulus-specific response selection accuracy. Adjusted-Savings Score was measured using the following equation: percent accuracy in Block 1 of Phase 2 ÷ percent accuracy in the last block of the Phase 1. Adjusted-Savings Score was significantly higher in PD patients tested ON compared to OFF medication. **B) Effect of PD and dopaminergic therapy on slope of learning stimulus-response associations.** Slope of learning served as a measurement of learning efficiency. To reiterate, slope was calculated using the block accuracy scores over the number of blocks in Phase 1 using the slope of the linear regression function (Microsoft Excel 2011). Slope of learning was significantly slower in PD patients tested ON compared to OFF dopaminergic medication. All values are presented separately for PD patients tested OFF medication, PD patients tested ON medication, and control participants tested in the sessions designated as ON and OFF

though control did not actually receive dopaminergic therapy. Error bars represent standard error of the mean.

* $p < 0.05$.

2.3.2 FMRI data

Significant activations in contrasts of interest are presented in Tables 2.3-7 and Figures 2.4 and 2.6. Contrasts collapsing across Group and Medication Session are reported at a significance level of $q < 0.05$ FDR corrected at the voxel level. Contrasts examining patients with PD versus healthy controls, as well as exploring each group separately for OFF-ON effects are reported at a significance level of $p \leq 0.001$ for predicted striatal regions, uncorrected for multiple comparisons.

2.3.2.1 Groups and medication sessions collapsed

Stimulus-Response Decision Events: Significant activity in the right dorsal caudate occurred during the Stimulus-Response Decision relative to Rest in Phase 1 (*peak coordinates:* 12, 5, 5; $t=5.76$, $q < 0.001$; Figure 2.4A). Significant right dorsal caudate activity also occurred in the Stimulus-Response Decision minus Feedback contrast in Phase 1 (*peak coordinates:* 12, 5, 2; $t=7.51$, $q < 0.001$; Figure 2.4B). When Stimulus-Response Decision Events were compared to Rest in Phase 2, significant activity in the left dorsal caudate (*peak coordinates:* 15, -1, 14; $t=4.76$, $q=0.015$; Figure 2.4C) occurred. DS was preferentially recruited during the Stimulus-Response Decision Event, in both Phases 1 and 2, replicating our previous findings (Nole M. Hiebert, Vo, et al., 2014).

Table 2.3 Significant brain activations in contrasts of interest collapsed across Group (PD and control) and Medication (OFF and ON) reported in MNI space.

Contrast	Anatomical Area	Cluster Size	t	q^*	x, y, z
<u>Phase 1: SR Events</u>					
SR minus rest	Right dorsal caudate	75	5.76	<0.001	12, 5, 5
	Right lingual gyrus	6928	12.33	<0.001	6, -85, -7
	Left paracingulate gyrus	427	6.62	<0.001	-3, 20, 44
	Right middle frontal gyrus	285	6.55	<0.001	48, 32, 32

SR minus FB	Right dorsal caudate	**	7.51	<0.001	12, 5, 2
	Left occipital fusiform gyrus	3471	13.70	<0.001	-30, -76, -16
	Right postcentral gyrus	299	4.89	<0.001	36, -31, 41
<u>Phase 2: SR Events</u>					
SR minus Rest	Right dorsal caudate	105	4.76	0.015	15, -1, 14
	Right lateral occipital cortex	3567	9.49	<0.001	42, -73, -10
	Right precentral gyrus	1011	5.40	<0.001	54, 11, 35
	Left precentral gyrus	1713	5.05	<0.001	-48, 5, 29
<u>Phase 1: FB Events</u>					
FB minus rest	Left postcentral gyrus	389	7.55	<0.001	-39, -28, 47
	Right postcentral gyrus	299	4.89	<0.001	36, -31, 41
FB minus SR	No Suprathreshold activations				
FB Correct minus Incorrect	Right nucleus accumbens	150	4.87	0.007	18, 11, -7
	Left nucleus accumbens	123	4.49	0.016	-18, 11, -1
FB Incorrect minus Correct	No suprathreshold activations				

Cluster size is reported in voxels. *Significance values are reported at $q < 0.05$ FDR corrected at the voxel level. Coordinates are reported in MNI space. Striatal regions are presented first and highlighted in each contrast. **Cluster size unobtainable as peak coordinates are within a larger cluster. N.B. SR – Stimulus-Response Decision Events; FB – Feedback Events.

Feedback Learning Events: Correct and incorrect Feedback Events combined relative to Rest or relative to Stimulus-Response Decision Events revealed no significant striatal activations. Significant VS but not DS activity occurred in the left (*peak coordinates:* -18, 11, -1; $t=4.49$, $q=0.016$; Figure 2.4D), and right nucleus accumbens (*peak coordinates:* 18, 11, -7; $t=4.87$, $q<0.007$; Figure 2.4D), in the correct minus incorrect feedback contrast, however. No significant striatal region was active in the reverse (i.e., incorrect minus correct) contrast.

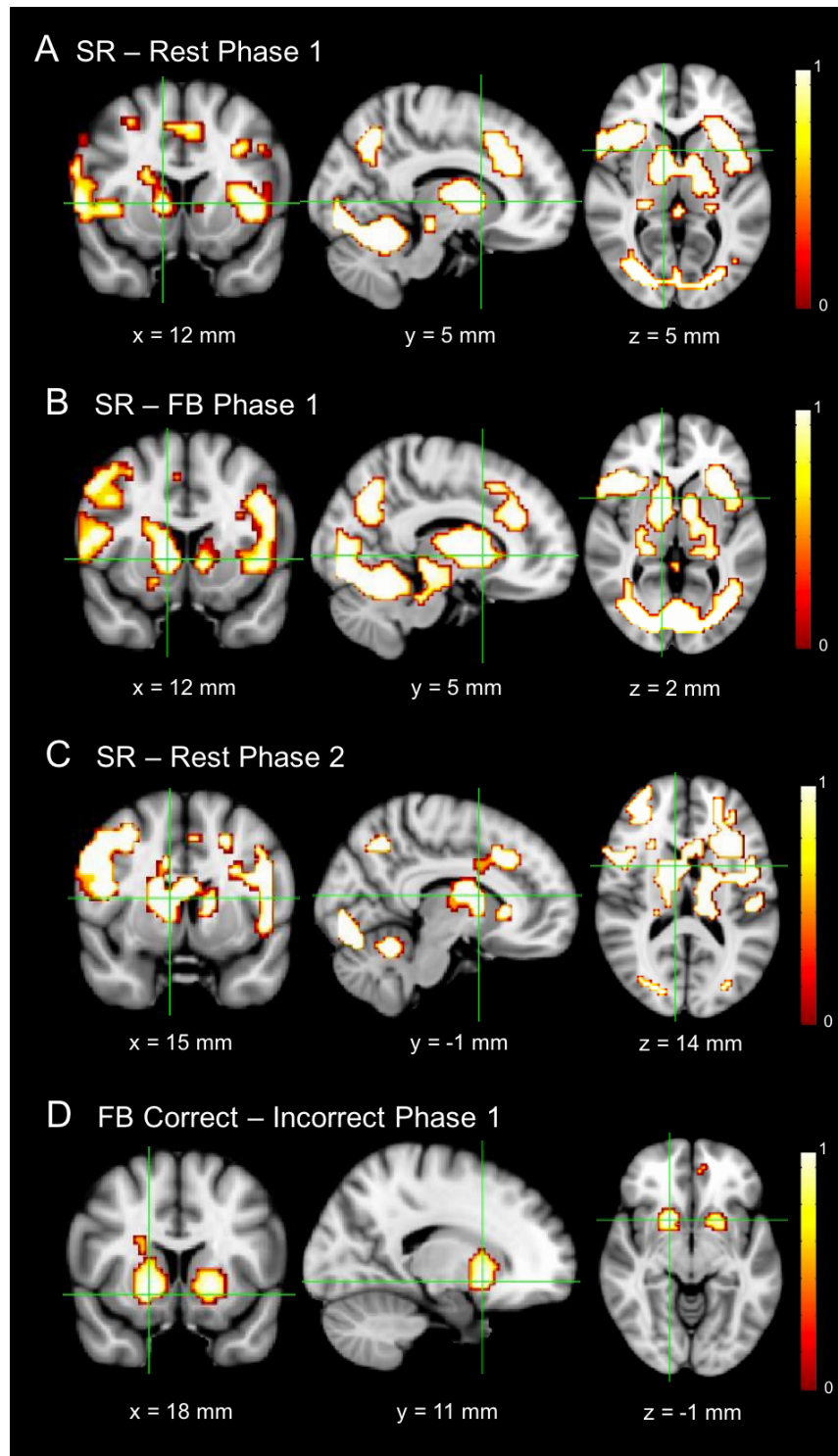


Figure 2.4 Significant activations in contrasts collapsing across Group (PD and control) and medication status (OFF and ON).

Activation maps are presented at a threshold of $p \leq 0.001$ uncorrected for multiple comparisons, as well as centred on the striatal activation for visualization purposes. **A)** BOLD signal for Stimulus-Response Decision Events minus Rest across all blocks in Phase 1. The cross-hairs are centred on the significant activity that arose in the right dorsal caudate (*peak coordinates*: 12, 5, 5; $t = 5.76$, $q < 0.001$). **B)** BOLD signal for Stimulus-Response Decision minus Feedback Events across all blocks in Phase 1. The cross-hairs are centred on the significant cluster that arose in the right dorsal caudate (*peak coordinates*: 12, 5, 2; $t = 7.51$, $q < 0.001$). **C)** BOLD signal for Stimulus-Response Decision minus Rest Events across all blocks in Phase 2. The cross-hairs are centred on the significant activity that arose in the left dorsal caudate (*peak coordinates*: 15, -1, 14; $t = 4.76$, $q = 0.015$). **D)** BOLD signal for correct minus incorrect Feedback Events across all blocks in the Phase 1. The cross-hairs are centred on the significant activation that arose in the right nucleus accumbens (*peak coordinates*: 18, 11, -7; $t = 4.87$, $q < 0.007$). A significant cluster was also present in the left nucleus accumbens (*peak coordinates*: -18, 11, -1; $t = 4.49$, $q = 0.016$). N.B. SR – Stimulus-Response Decision Events and FB – Feedback Events in the figure.

2.3.2.2 Bayesian analysis

Beta values extracted from the two right and left anatomical DS and VS ROIs from key contrasts of interest involving Stimulus-Response Decision and Feedback Events (Table 4). Bayes' factor one-sample t -tests were conducted on beta values for each of the four ROIs extracted from each contrast of interest. In this analysis, a Bayes' factor of less than three is considered to significantly support the null hypothesis (Dienes, 2014).

Phase 1 Stimulus-Response Decision Events: Contrasting Stimulus-Response Decision minus Rest events for Phase 1 in PD patients, collapsed across Medication session revealed a Bayes' factor greater than three in the Right DS in both PD patients and control participants, separately (Right DS: $BF_{10} = 8.705$; Right DS: $BF_{10} = 3.691$, respectively). Bayes' factor for Right VS was also greater than three in PD patients only ($BF_{10} = 3.124$).

Phase 2 Stimulus-Response Decision Events: Contrasting Stimulus-Response Decision minus Rest events for Phase 2, collapsed across Medication session, revealed Bayes' factors greater than three in Left DS for PD patients ($BF_{10} = 4.911$), and Right DS for control participants ($BF_{10} = 6.870$).

Phase 1 Correct minus Incorrect Feedback Events: In the correct minus incorrect Feedback Events, collapsed across Medication session, PD patient's Bayes' factors for DS ROIs were far below three, indicating that beta values in these regions were not significantly above

zero (Left DS: $BF_{10} = 0.905$; Right DS $BF_{10} = 0.963$). In contrast, Bayes' factors for VS ROIs were above three indicating that VS is preferentially activated during these events with beta values significantly above zero (Left VS: $BF_{10} = 8.666$; Right DS: $BF_{10} = 7.022$). A similar pattern arose in control participants (Left DS: $BF_{10} = 0.129$; Right DS $BF_{10} = 0.117$; Left DS: $BF_{10} = 4.843$; Right DS $BF_{10} = 7.042$).

Table 2.4 Bayes' factors for contrasts of interest in Phases 1 and 2.

Contrasts	Left DS	Right DS	Left VS	Right VS
PD patients collapsed across Medication session				
i) Stimulus-Response Decision Events in Phase 1	1.768	8.705	0.561	3.124
ii) Stimulus-Response Decision Events in Phase 2	4.911	2.396	1.222	0.363
iii) Correct minus Incorrect Feedback Events minus Rest in Phase 1	0.905	0.963	8.666	7.022
Control participants collapsed across Medication session				
i) Stimulus-Response Decision Events in Phase 1	1.505	3.691	0.827	1.003
ii) Stimulus-Response Decision Events in Phase 2	2.684	6.870	0.625	0.625
iii) Correct minus Incorrect Feedback Events minus Rest in Phase 1	0.129	0.117	4.843	7.042

Bayes' factors (BF_{10}) are presented for each of the four anatomical ROIs for contrasts of interest. Bayes' factors less than three indicate that the results strongly support the null hypothesis, that activation is not greater than zero.

2.3.2.3 Brain-behaviour correlations: PD and controls separately

Two right and left VS and two right and left DS ROIs were employed in Nole M. Hiebert, Vo, et al. (2014)—the study in which the current cognitive paradigm was first explored with fMRI in healthy young controls. BOLD signal in these ROIs was correlated with our behavioural measures of stimulus-response decision accuracy and feedback-based learning efficiency. The Adjusted-Savings Score served as our measure of decision accuracy, and the slope of change in correctly associating stimuli and responses was used our measure of stimulus-response association learning.

Striatum and response-selection decisions: Beta values from each of the ROIs were correlated with adjusted-savings scores in OFF and ON sessions for PD patients and healthy controls separately. For PD patients, beta values extracted during Stimulus-Response Decision Events in the Phase 2 from the left dorsal caudate ROI positively correlated with adjusted savings scores ($r=0.35$, $t=2.19$, $p=0.035$; Figure 2.5A). For control participants, beta values extracted from the right dorsal putamen ROI significantly correlated with adjusted savings ($r=0.35$, $t=2.18$, $p=0.042$; Figure 2.5B). Neither of the VS ROIs correlated with Adjusted-Savings Scores in either the PD or the healthy control group.

Striatum and learning from feedback: Beta values from each of the VS and DS ROIs were correlated with slope of learning in the OFF and ON sessions combined for PD patients and healthy controls separately. A significant positive correlation arose between slope and beta value in the right ventral caudate ROI ($r=0.34$, $t=2.17$, $p=0.037$; Figure 2.5C) for PD patients only. No other ROIs correlated significantly with slope. Of greatest significance given our aim of directly testing the notion that DS mediates stimulus-response learning, levels of activation in our DS ROIs did not correlate with the slope of stimulus-response learning in either the PD or control groups.

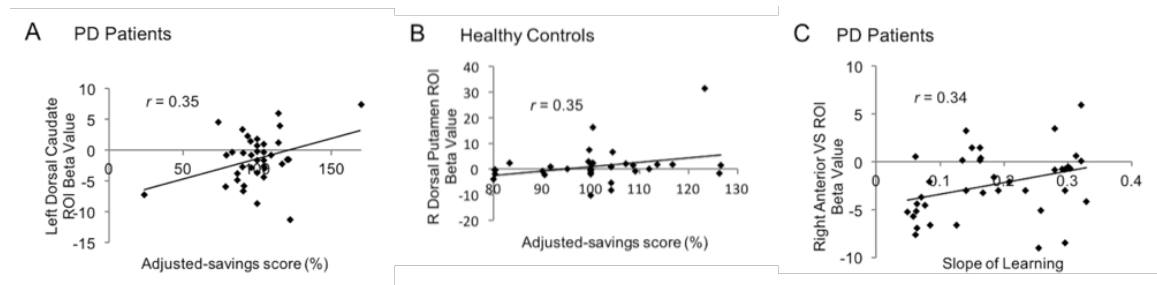


Figure 2.5 Brain-behaviour correlations between BOLD signal in ROIs and measures of learning and stimulus-specific response selection.

A) Beta values extracted from the left dorsal caudate ROI in the Stimulus-Response Decision Events minus Rest contrast correlated positively and significantly with adjusted-savings in patients with PD on and off medication. **B)** Beta values extracted from the right dorsal putamen ROI significantly correlated with adjusted savings in healthy controls. **C)** Beta values extracted from the right anterior VS ROI in the Feedback Events minus Rest contrast, correlated positively and significantly with slope of learning in patients with PD on and off medication.

2.3.2.4 PD patients: OFF versus ON sessions

Stimulus-Response Decision events OFF minus ON: There was no preferential activity in the striatum in this contrast for Phase 1 or 2 data.

Stimulus-Response Decision events PD ON minus OFF: Significant left (*peak coordinates:* -24, 5, 11; $t=3.86$, $p<0.001$) and right dorsal putamen (*peak coordinates:* 21, 2, 14; $t=3.83$, $p<0.001$) activity arose in the ON relative to OFF Session for Stimulus-Response Decision Events in Phase 1 (Figure 2.6A). A significant peak of activity in the right nucleus accumbens (*peak coordinates:* 12, 11, -10; $t=4.40$, $p<0.001$) also arose. Significant left (*peak coordinates:* -12, 11, 14; $t=3.68$, $p<0.001$) and right dorsal caudate (*peak coordinates:* 6, 2, 20; $t=3.45$, $p<0.001$) activity occurred in the ON relative to OFF Session for the Stimulus-Response Decision contrast in Phase 2 (Figure 2.6B). Overall, these results reveal a task-specific, dopaminergic therapy-related DS BOLD signal enhancement for decision enactment.

Feedback learning events OFF minus ON: When Feedback Events were investigated in the OFF minus ON contrast, significantly greater activity occurred in the left ventral putamen (*peak coordinates:* -21, 5, -1; $t=3.41$, $p<0.001$; Figure 2.6C), suggesting that medication dampened VS activity.

Feedback learning events ON minus OFF: No significant activity occurred in this contrast.

Feedback learning correct minus incorrect events OFF minus ON: Significantly greater activity occurred in the right ventral putamen, extending into the nucleus accumbens and ventral caudate (*peak coordinates:* 18, 11, -4; $t=3.15$, $p=0.001$) when PD patients were tested off relative to on dopaminergic therapy. Again, this suggests that dopaminergic therapy attenuates VS activity, consistent with the dopamine overdose hypothesis.

Feedback learning correct minus incorrect events ON minus OFF: No significant striatal activity occurred in this contrast.

Table 2.5 Significant brain activations in contrasts of interest for patients with PD OFF versus ON dopaminergic medication reported in MNI space.

Contrast	Anatomical Area	Cluster Size	<i>t</i>	<i>p</i> *	<i>x, y, z</i>
<u>Phase 1: SR Events</u>					
OFF minus ON SR events	No suprathreshold activations				
ON minus OFF SR events	Right dorsal putamen	15	3.83	<0.001	21, 2, 14
	Left dorsal putamen	36	3.86	<0.001	-24, 5, 11
	Right nucleus accumbens	**	4.40	<0.001	12, 11, -10
<u>Phase 2: SR Events</u>					
OFF minus ON SR events	No suprathreshold activations				
ON minus OFF SR events	Left dorsal caudate	43	3.68	<0.001	-12, 11, 14
	Right dorsal caudate	61	3.45	<0.001	6, 2, 20
<u>Phase 1: FB Events</u>					
OFF minus ON FB events	Left ventral putamen	14	3.41	<0.001	21, 5, -1
ON minus OFF FB events	No suprathreshold activations				
OFF minus ON Correct minus Incorrect FB events	Left ventral putamen	178	3.15	0.001	-21, 20, -1
ON minus OFF Correct minus Incorrect FB events	No suprathreshold activations				

Cluster size is reported in voxels. *p* values are reported at a significance level of at $p \leq 0.001$ uncorrected at the voxel level. Coordinates are reported in MNI space. Striatal regions are presented first and highlighted in each contrast. **Cluster size unobtainable as peak coordinates are within a larger cluster. N.B. SR – Stimulus-Response Decision Events; FB – Feedback Events.

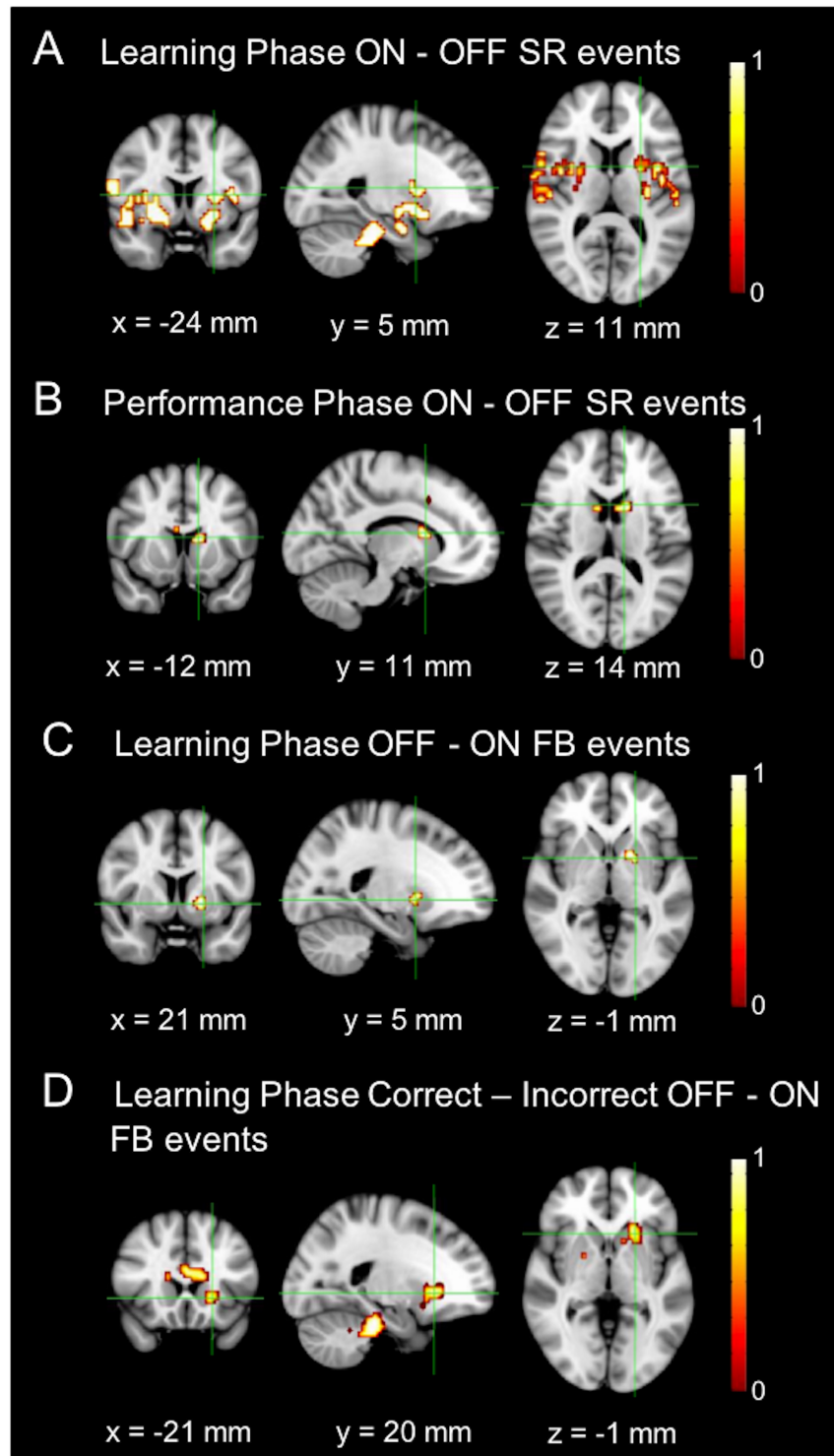


Figure 2.6 Significant activations in contrasts examining only PD patients ON and OFF dopaminergic medication.

Activation maps are presented at a threshold of $p \leq 0.001$ uncorrected for multiple comparisons and centred on the striatal activation. **A)** BOLD signal for ON minus OFF Stimulus-Response Decision Events across all blocks in Phase 1. The cross-hairs are centred on the significant cluster that arose in the left dorsal putamen (*peak coordinates*: -24, 5, 11; $t = 3.86$, $p < 0.001$). Significant activity also arose in the right dorsal putamen (*peak coordinates*: 21, 2, 14; $t = 3.83$, $p < 0.001$) and right nucleus accumbens (*peak coordinates*: 12, 11, -10; $t = 4.40$, $p < 0.001$). **B)** BOLD signal for ON minus OFF Stimulus-Response Decision Events across all blocks in Phase 2. The cross-hairs are centred on the significant activity that arose in the right dorsal caudate (*peak coordinates*: -12, 11, 14; $t = 3.68$, $p < 0.001$). Significant activity also occurred in the left dorsal caudate (*peak coordinates*: 6, 2, 20; $t = 3.45$, $p < 0.001$). **C)** BOLD signal for OFF minus ON Feedback Events across all blocks in the Phase 1. The cross-hairs are centred on the significant cluster in the left ventral putamen (*peak coordinates*: 21, 5, -1; $t = 3.41$, $p < 0.001$). **D)** BOLD signal for OFF minus ON correct minus incorrect Feedback Events across all blocks in Phase 1. The cross-hairs are centred on the cluster of activation in the left ventral putamen (*peak coordinates*: -21, 20, -1; $t = 3.15$, $p = 0.001$). N.B. SR – Stimulus-Response Decision Events and FB – Feedback Events in the figure.

2.3.2.5 Healthy control: ON versus OFF sessions

There was no preferential activity in the striatum in any contrasts comparing OFF and ON sessions in healthy controls. This is as expected given that healthy control participants did not actually receive dopaminergic therapy in any condition and their data were simply analyzed to correspond to the OFF-ON state of the PD patient to whom they were matched.

Table 2.6 Significant brain activations in contrasts of interest for healthy controls in the OFF versus ON groups

Contrast	Anatomical Area	Cluster Size	t	q^*	x, y, z
<u>Phase 1: SR Events</u>					
OFF minus ON SR events	No suprathreshold activations				
ON minus OFF SR events	No suprathreshold activations				
<u>Phase 2: SR Events</u>					
OFF minus ON SR events	No suprathreshold activations				
ON minus OFF SR events	No suprathreshold activations				
<u>Phase 1: FB Events</u>					
OFF minus ON FB events	No suprathreshold activations				
ON minus OFF FB events	No suprathreshold activations				
OFF minus ON Correct minus Incorrect FB events	No suprathreshold activations				
ON minus OFF Correct minus Incorrect FB events	No suprathreshold activations				

Cluster size is reported in voxels. p values are reported at a significance level of $p \leq 0.001$ uncorrected for multiple comparisons. p values are reported at the voxel level. Coordinates are reported in MNI space. Striatal regions are presented first and highlighted in each contrast. **Cluster size unobtainable as peak coordinates are within a larger cluster. N.B. SR – Stimulus-Response Decision Events; FB – Feedback Events.

2.3.2.6 PD versus controls

OFF Stimulus-Response Decision Events: Contrasting PD minus control revealed no significant striatal activity in Phases 1 or 2. However, in the control minus PD contrast, controls exhibited significantly greater activation in the right dorsal caudate nucleus (*peak coordinates:* 6, 5, 5; $t=3.21$, $p<0.001$) than PD patients who were in the OFF state in Phase 1. No significant activity arose in Phase 2 comparing control and PD participants.

ON Stimulus-Response Decision Events: When PD patients were corrected with exogenous dopaminergic therapy in the ON Session, no significant striatal activity arose in the PD minus control or control minus PD contrasts. In Phase 2, in fact, significantly greater activation arose in the left (*peak coordinates:* -12, 11, 17; $t=3.75$, $p<0.001$) and right dorsal caudate nuclei (*peak coordinates:* 6, 5, 20; $t=3.35$, $p<0.001$) for PD patients relative to healthy age-matched controls. Recall that age-matched controls did not actually receive dopaminergic therapy and rather their data were simply analyzed to correspond to the dopaminergic state of the PD patient to whom they were matched. No significant striatal activity occurred in the reverse contrast (i.e., control minus PD).

OFF Feedback Events: No significant striatal activity arose for OFF sessions in the PD minus control contrast. A significant cluster arose in the left ventral caudate (*peak coordinates:* -18, 23, -1; $t=3.66$, $p<0.001$) in the control minus PD contrast.

ON Feedback Events: Contrasting PD minus control revealed no significant striatal activity. However, in the control minus PD contrast, significant activity arose in the left ventral putamen (*peak coordinates:* -18, 5, -1; $t=2.31$, $p=0.001$).

Table 2.7 Significant brain activations in contrasts of interest for patients with PD versus control participants OFF and ON dopaminergic medication reported in MNI space.

Contrast	Anatomical Area	Cluster Size	<i>t</i>	<i>p</i> *	<i>x, y, z</i>
<u>Phase 1: SR Events</u>					
PD OFF minus control OFF	No suprathreshold activations				
control OFF minus PD OFF	Right dorsal caudate	2	3.21	0.001	6, 5, 5
PD ON minus control ON	No suprathreshold activations				
control ON minus PD ON	No suprathreshold activations				
<u>Phase 2: SR Events</u>					
PD OFF minus control OFF	No suprathreshold activations				
control OFF minus PD OFF	No suprathreshold activations				
PD ON minus control ON	Left dorsal caudate	8	3.75	<0.001	-12, 11, 17
control ON minus PD ON	No suprathreshold activations				
<u>Phase 1: FB Events</u>					
PD OFF minus control OFF	No suprathreshold activations				
control OFF minus PD OFF	Left ventral caudate	29	3.66	<0.001	-18, 23, -1
PD ON minus control ON	No suprathreshold activations				
control ON minus PD ON	No suprathreshold activations				

Cluster size is reported in voxels. *p* values are reported at a significance level of at $p \leq 0.001$ uncorrected at the voxel level. Coordinates are reported in MNI space. Striatal regions are presented first and highlighted in each contrast. N.B. SR – Stimulus-Response Decision Events; FB – Feedback Events.

2.4 Discussion

In both Phases 1 and 2 across Sessions 1 and 2, we found that DS activity correlated preferentially with Stimulus-Response Decision Events and *not* with Feedback Events. It is notable that feedback-based learning was precluded by the omission of feedback in Phase 2. DS activation persisted in Phase 2 nonetheless, further casting doubt on DS's role in feedback-based learning. We also found that beta values in DS ROIs (i.e., left dorsal caudate in the PD group; left dorsal putamen in the healthy controls) in Phase 2 correlated with the accuracy of stimulus-specific response selections (i.e., Adjusted Savings Score), intended as our behavioural measure of decision making. Most significant, given our aim of critically testing DS's role in stimulus-response learning, intensity of activation in DS

ROIs did not correlate with our behavioural measure of learning efficiency in either the PD or control group. These results implicate DS in stimulus-specific response decisions entirely replicating our main finding in Nole M. Hiebert, Vo, et al. (2014), in which we used this paradigm in healthy young controls.

In contrast, in Phase 1 only, VS was preferentially activated during correct relative to incorrect Feedback Events. The Feedback Event in each trial is the moment during which learning stimulus-response relations occurs through deterministic outcome information. Further, we found that beta values in a VS ROI (i.e., right ventral caudate in the PD group) correlated significantly with Learning Slope, our measure of learning efficiency but not with Adjusted-Savings Score, our measure of decision accuracy. These findings support a role for VS in stimulus-response association learning also replicating our results with healthy young controls in Nole M. Hiebert, Vo, et al. (2014).

In agreement with our frequentist behavioural and fMRI analyses presented above, using Bayesian analyses we found that in both PD patients and healthy controls investigated separately, activation in DS ROIs correlated significantly with Stimulus-Response Decision Events in both Phases 1 and 2 of the experiment. In contrast and of critical importance given the main aim of our study, with Bayesian analysis, we confirmed that activation in DS ROIs was not significantly associated with stimulus-response association learning during Feedback events (i.e., the null hypothesis was supported). VS ROI beta values were significant during the Feedback event using Bayesian analyses concordant with our other investigations in suggesting that the VS mediates stimulus-response association learning through feedback.

Strongly supporting these distinct cognitive roles for DS and VS, PD patients evidenced impaired response-selection performance, using the Adjusted-Savings Score, off medication, which was normalized by dopaminergic therapy. Conversely, efficiency of learning stimulus-response associations, assessed by our slope of learning measure, was equivalent for PD patients and healthy controls, off dopaminergic medication. However, the slope of learning was worsened by dopaminergic medication in our PD group. Recall that in PD, DS is dopamine depleted and its functions are impaired in the OFF state. DS

functions are remediated by dopaminergic therapy. In contrast, VTA-innervated brain areas such as VS are relatively dopamine replete and their functions are normal at baseline. Their functions are actually worsened due to dopamine overdose in the ON state (Cools, 2006). Entirely confirming our interpretation of the behavioural patterns, DS signal associated with the Stimulus-Response Decision Event was enhanced by dopaminergic medications in PD patients using within-subject contrasts. In contrast, Feedback Event-related VS signal was depressed by exogenous dopamine therapy (i.e., dopamine overdose effect).

In contrast to our findings in PD, for healthy controls who did not actually receive dopaminergic therapy but whose data were analyzed to correspond to the ON-OFF order of the PD patients to whom they were matched, there were no response-selection accuracy or learning efficiency differences, or differential patterns of fMRI activity comparing the ON versus OFF sessions, as expected. These findings in controls suggest that differences observed for PD patients were not the result of order, practice, or stimulus effects across the OFF and ON sessions.

Bolstering our within-subject patterns in PD, between-group comparisons revealed that DS activation in PD patients was reduced relative to DS activation in healthy age-matched controls in the OFF state during Stimulus-Response Decision Events. DS activation between PD and healthy controls was equivalent, however, in the ON Sessions, once PD patients were medicated with dopaminergic therapy. Further, VS, but not DS, activation was decreased for PD patients relative to healthy controls in the ON Session in the exact region (i.e., left ventral putamen) where dopaminergic therapy attenuated VS activation in the PD OFF-ON contrast, consistent with the dopamine overdose hypothesis.

2.4.1 Cognitive functions mediated by striatum

The striatum mediates cognitive functions (Atallah et al., 2007; Alex A. MacDonald et al., 2014) in addition to its better-known role in motor control. We independently assessed response-selection decisions and stimulus-response learning, using behavioural measures and distinct fMRI events. We aimed to disentangle neural substrates specifically mediating these different cognitive processes. DS activation correlated with stimulus-response

decisions whereas VS signal arose preferentially during delivery of feedback through which stimulus-response associations were learned. This entirely replicates our results in healthy, young individuals (Nole M. Hiebert, Vo, et al., 2014). Beyond correlational evidence, however, in PD patients, we found clear double dissociations in DS- and VS-mediated behaviour and preferential neural activity contrasting the OFF and ON dopaminergic therapy states. PD patients demonstrated *enhanced* stimulus-specific response-selection accuracy and DS activity during Stimulus-Response Decision Events, compared to *attenuated* stimulus-response association learning and VS activation during Feedback Events, on relative to off dopaminergic therapy. This pattern of results provides strong support for the concept that DS mediates response-selection decisions and not learning—the latter being mediated by VS rather.

Our results are completely at odds with the large literature attributing feedback-based learning to DS (Balleine, Liljeholm, & Ostlund, 2009; Hart, Leung, & Balleine, 2013; Yin & Knowlton, 2006). A potential explanation for the long-standing association of DS with stimulus-response association learning, despite increasing numbers of contradictory results (Atallah et al., 2007; Grahn, Parkinson, & Owen, 2008; Ohira et al., 2010; Reiss et al., 2005), relates to the common confounding of learning and decision-making processes (Jessup & O'Doherty, 2011; McDonald & Hong, 2004). In behavioural studies, learning is generally measured by the accuracy of stimulus-specific response selections that are provided as evidence that learning has occurred. Poor performance therefore could be the result of failing either to learn stimulus-response associations or to correctly select responses based on these learned associations. In fMRI studies, a) enacting a response when presented with a stimulus, and b) learning from feedback, are typically treated as a single event with all significantly-activated brain regions ascribed a role in learning *per se* (Dobryakova & Tricomi, 2013; Jessup & O'Doherty, 2011; Poldrack et al., 1999). By separately assessing response-selection decisions and learning, our approach aimed to resolve the discrepancy between studies that involve DS in feedback-based learning (Boettiger & D'Esposito, 2005; O'Doherty et al., 2004) versus those in PD patients (Swainson et al., 2000; Vo et al., 2014), and participants with DS lesions (Ell, Marchant, & Ivry, 2006; Exner et al., 2002) that dispute the notion that DS mediates stimulus-response learning.

Our findings integrate with a growing literature favouring a role for DS in decision making rather than learning *per se*. In neuroimaging studies, DS activity consistently remains significantly increased above baseline *after* sequences (Reiss et al., 2005), categorization rules (Helie, Roeder, & Ashby, 2010; Seger, Peterson, Cincotta, Lopez-Paniagua, & Anderson, 2010), stimulus–reward (Daw & Doya, 2006; Seger et al., 2010), and response–reward associations (Ohira et al., 2010) are well learned. Additionally, DS frequently correlates with response selections, particularly when an element of deliberation is required (N. M. Hiebert, Owen, Seergobin, & MacDonald, 2017), even in contexts *devoid of new learning* (Grahn et al., 2008), such as in the Stroop task (Ali, Green, Kherif, Devlin, & Price, 2010), and in making numeric magnitude judgments (P. A. MacDonald et al., 2011). This activation profile is inconsistent with a brain region mediating learning *per se* and is more in line with one that underlies decisions.

Our results, in contrast suggest that VS mediates learning stimulus-response associations. Replicating our previous findings (Nole M. Hiebert, Vo, et al., 2014), VS signal occurred specifically during the Feedback Event and correlated with efficiency of learning assessed with slope measure. Further, learning efficiency and VS activation were reduced for PD patients on relative to off dopaminergic therapy, suggesting that VS, a VTA-innervated structure, was overdosed by exogenous dopamine. This result fits with the larger literature implicating VS in forms of implicit learning, such as reward (Camara, Rodriguez-Fornells, & Munte, 2010), stimulus-stimulus (P. A. MacDonald et al., 2011), sequence (Ghilardi et al., 2007), motor sequence (Feigin et al., 2003), and category learning (Shohamy, Myers, Geghman, Sage, & Gluck, 2006).

2.4.2 Effect of dopaminergic therapy on cognition in PD

The notion that abnormalities in dopamine across different brain regions cause cognitive as well as motor symptoms in PD has long been considered (Brown & Marsden, 1984; Gotham, Brown, & Marsden, 1988). Cognitive functions mediated by SNc-innervated brain regions such as the DS are expected to be improved by dopaminergic therapy, whereas the opposite pattern is expected for VTA-supplied brain regions such as VS in PD. This is due to different rates and degrees of degeneration of dopamine-producing neurons

in SNc and VTA in PD. This theoretical framework successfully explains complex behavioural patterns in PD (Cools, 2006; Vaillancourt, Schonfeld, Kwak, Bohnen, & Seidler, 2013). This framework is prevalent and effectively accounts for behavioural patterns across a large number of PD studies (Cools, 2006; Dirnberger & Jahanshahi, 2013; Vaillancourt et al., 2013). Studies that fully support these concepts in a single experiment are lacking, however. Here, we provide direct support for this framework for understanding cognitive patterns in PD. We show *for the first time* that dopaminergic therapy *simultaneously* a) improved DS-mediated response selection and boosted DS signal and b) impaired VS-mediated stimulus-response learning and attenuated VS activity. Though previous investigations provide evidence of improved DS function and increased DS activity (Aarts et al., 2014) or impaired functions mediated by VTA-innervation brain regions and corresponding reduced signal (Aarts et al., 2014; Cools, Lewis, Clark, Barker, & Robbins, 2007; Kwak, Müller, Bohnen, Dayalu, & Seidler, 2012; Van Eimeren et al., 2009), none have provided evidence of *these simultaneous and opposite effects* within the same participants, though a number of studies aimed to do so (Aarts et al., 2014; Argyelan et al., 2008; Shiner et al., 2012; Van Eimeren et al., 2009).

2.4.3 Conclusions

Our findings dispute the prevalent notion that DS mediates stimulus-response learning. We showed that DS mediates response selections whereas VS underlies feedback-based learning in PD patients and healthy age-matched controls. This study provides strong support for the view that DS has been erroneously ascribed a role in feedback-based, stimulus-response learning due to methodology that confounds learning and response-selection processes. Our findings integrate with a growing literature favouring a role for DS in decision performance rather than learning *per se*.

2.5 References

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Chapter 3

3 Role of baseline dorsal and ventral striatum activity in stimulus-response learning in patients with obsessive compulsive disorder

Dorsal striatum (DS) has long been implicated in stimulus-response learning, though recent results challenge this notion. We have proposed that discrepant findings arise because stimulus-response learning methodology generally confounds learning and response selection processes. We implement a design that allows DS and ventral striatum (VS) to be assessed within the same experimental paradigm, with these conditions interleaved with one another. Obsessive compulsive disorder (OCD) is a prevalent psychiatric disorder characterized by obsessions and compulsions. Studies investigating symptomatology and cognitive deficits in OCD frequently implicate the DS and VS. The main aim of this study was to dissociate the roles of DS and VS in decision making and stimulus-response learning in patients with OCD to a) better clarify DS and VS function, as well as b) understand how DS and VS dysfunction might lead to characteristic symptoms. We found that patients with OCD ($n=14$) and healthy age-matched controls ($n=15$) exhibited decision making deficits and learned associations slower compared to controls. Along with these behavioural deficits, OCD patients had reduced task-relevant activity in DS and VS, compared to controls. In healthy controls, activity in DS arose during response selection and correlated with our measure of decision making and not learning, however. When rest activity was separately investigated, no differences were noted in DS but activity in VS was significantly higher in patients with OCD compared to controls. Additionally, the level of activity in VS negatively correlated with the severity of compulsions in patients with OCD. OCD patients with higher baseline VS activity had less severe compulsions, potentially because tension-reduction related to compulsion-enactment could not be encoded as rewarding when VS was chronically hyperactive. This study suggests that DS does not mediate stimulus-response learning and sheds light on the cognitive deficits and symptoms experienced by patients with OCD.

3.1 Introduction

Obsessive compulsive disorder (OCD) is a psychiatric disorder prevalent in 1.2% of American adults and is described by the National Institute of Mental Health as typically chronic with a gradual onset (Association, 2013; Sasson et al., 1997). OCD is characterized by two major symptoms: obsessions and compulsions (Association, 2013; Sasson et al., 1997). The former is defined as disturbing thoughts, urges, or impulses, and the latter as recurring behaviours or mental acts that individuals affected by the disorder feel driven to perform (Association, 2013).

Patients with this disorder exhibit diversity in severity, however, the symptoms tend to follow a general order: obsessive thoughts, anxiety, compulsions, and temporary relief with reduction in anxiety (Association, 2013; Sasson et al., 1997). For example, with respect to sanitization, patients may have an irrational fear of being contaminated by germs, resulting in illness or death (Bokor & Anderson, 2014; Mataix-Cols et al., 2004). Anxiety often ensues and patients feel driven to carry out certain tasks to reduce their distress. The individual may wash or clean repetitively until a “feeling” of cleanliness is achieved, whereas a typical individual may wash until observing that they are clean. Completion of the respective compulsions result in temporary relief and the cycle repeats. Patients spend a substantial amount of time with their obsessions and carrying out compulsions, and this can be costly to maintaining jobs and relationships (Torres et al., 2015).

The basal ganglia, a group of subcortical nuclei, is commonly known to be impaired in movement disorders (i.e., Parkinson’s disease). However, the striatum, the input region of the basal ganglia, is increasingly implicated in cognitive functions (Gotham, Brown, & Marsden, 1988; P. A. MacDonald & Monchi, 2011). The striatum can be divided functionally into two regions, the dorsal and ventral striatum (DS and VS, respectively), based on independent dopaminergic and glutamatergic inputs, vascular supplies, and functions (Feeke & Cassell, 2006; Kish, Shannak, & Hornykiewicz, 1988; Tziortzi et al., 2014). DS encompasses the majority of the caudate nucleus and putamen, and VS is comprised of the NAcc and ventral regions of the caudate nucleus and putamen (P. A. MacDonald & Monchi, 2011).

The view that DS is critical for stimulus-response learning, is well-entrenched (Brovelli, Nazarian, Meunier, & Boussaoud, 2011; Chiu, Jiang, & Egner, 2017; Thompson RL, 1963; Yin & Knowlton, 2006). Despite the prevalence of this view, learning is often preserved in patients (Exner, Koschack, & Irle, 2002; Nole M. Hiebert, Seergobin, Vo, Ganjavi, & MacDonald, 2014; A. A. MacDonald et al., 2013; Vo et al., 2014) and animals (Atallah, Lopez-Paniagua, Rudy, & O'Reilly, 2007) with DS dysfunction.

Potentially underlying the discrepancies in the stimulus-response learning literature, response selection decisions and learning are often intrinsically confounded (Jessup & O'Doherty, 2011; McDonald & Hong, 2004). In stimulus-response learning experiments, trials generally proceed as follows: a) a stimulus is presented and participants perform a response, and b) feedback regarding response accuracy is provided. Feedback is the means through which stimulus-response associations are learned. Accuracy in selecting a learned response provides the learning measure. Performance depends upon both decision and learning processes. Failing either to acquire stimulus-response relations or to correctly select learned responses produces impaired performance. Further, in fMRI studies, a) deciding upon and enacting a response, and b) learning from feedback, are typically treated as a single event with all significantly activated brain regions ascribed a role in learning *per se* (Jessup & O'Doherty, 2011; Poldrack, Prabhakaran, Seger, & Gabrieli, 1999). Accordingly, some brain regions that might underlie response selection could erroneously be assigned a role in learning. The objective of the current study was to directly test this confound in patients with OCD, using a stimulus-response learning paradigm previously shown to separate decisions and learning, producing differential patterns of activity in DS and VS (Nole M. Hiebert, Vo, et al., 2014).

Notably, a number of studies have observed striatal changes in patients with OCD. It has been found that the VS in patients with OCD has a higher metabolism compared to controls at rest (Del Casale et al., 2011; Menzies et al., 2008), as well as in response to symptom-provoking stimuli using PET (Rauch, Jenike, Alpert, & et al., 1994). Interestingly, despite this baseline increase in activity, during VS-mediated reward-anticipation tasks, Figuee et al. (2011) reported a decreased change in VS activity in patients with OCD compared to controls.

In contrast, patients with OCD were found to exhibit decreased DS activity at rest and during DS-mediated tasks (Del Casale et al., 2011). Nakao et al. (2005) conducted a colour-word Stroop task, where colour words (i.e., Red, Blue, Green), are presented in font colours that are either congruent with the colour word (i.e., Red, Blue, Green), or incongruent with the colour word (i.e., Red, Blue, Green). Patients with OCD and healthy controls were instructed to name the colour of the font, rather than read the colour word while brain activity was simultaneously recorded using fMRI. Patients with OCD took longer to complete the Stroop task and did not exhibit significant activity in DS, as did the healthy controls. In this task, the role of DS has been shown to mediate inhibiting the response that is more salient (colour word) and outputting the visual, font colour information (Ali, Green, Kherif, Devlin, & Price, 2010; Coderre & van Heuven, 2013; Djamshidian, O'Sullivan, Lees, & Averbeck, 2011; Fera et al., 2007; Larson, Clayson, Primosch, Leyton, & Steffensen, 2015; C. M. MacLeod, 1991; C. M. MacLeod & MacDonald, 2000; Nakao et al., 2005; Wright & Wanley, 2003). DS deficits in patients with OCD result in poor cognitive flexibility and response inhibition that may lead to compulsive actions.

If DS mediates stimulus-response learning, it is predicted that a) DS activity will correlate with learning measures and with the moment when stimulus-response association learning occurs (i.e., the Feedback Event, when outcome information regarding response accuracy is provided), and b) learning will be diminished in patients with OCD and related to reduced DS activity compared to controls.

In contrast, if DS mediates stimulus-response decision performance and VS mediates stimulus-response association learning, as we expect, a) DS activity will correlate with accuracy of decision performance and with the moment when response selection occurs (i.e., the Stimulus-Response Decision Event), and b) accuracy of stimulus-specific decisions and DS signal will be poorer in patients with OCD compared to controls. Further, we predict that a) VS activity will correlate with learning measures and with the moment of learning during the Feedback Event, and b) efficiency of learning and VS task-related signal (i.e., processing of feedback through which stimulus-response associations are learned) will be diminished in patients with OCD compared to controls.

In turn, this task further allowed us to explore cognitive deficits in patients with OCD, relating them to the DS and VS in particular, as well as other brain regions that might cooperate with these striatal regions. Further, we planned to explore how striatal signals related to symptoms of OCD.

3.2 Materials and methods

3.2.1 Participants

Fourteen patients with OCD and 15 control participants completed the experiment. All patients with OCD were previously diagnosed by a licenced psychiatrist. All participants had no confounding neurological or psychiatric disorders. Patients abusing alcohol, prescription or street drugs, or taking cognitive-enhancing medications like donepezil, galantamine, rivastigmine, memantine, or methylphenidate were excluded from participating.

Mean group demographic, as well as cognitive and affective screen scores for all patients and controls were recorded (Table 3.1). The Yale-Brown Obsessive Compulsive Scale (YBOCS) was administered to patients with OCD to quantify the presence and severity of obsessive and compulsive symptoms. The YBOCS is scored yielding a total OCD severity score, an obsession sub-score and a compulsive sub-score.

3.2.2 Experimental Design

Each participant completed a stimulus-response task in which they learned to associate twelve abstract images with one of three button-press responses. These images, shown in Figure 3.1, were computer-generated with *GroBoto* (Braid Art Labs, Colorado Springs, USA). The task was administered within a 3 Tesla fMRI scanner to observe concurrent regional activity within the striatum.



Figure 3.1 Abstract images presented in the experiment.

Images were associated with a button pressed by the index, middle, or ring finger buttons.

Figure 3.2 demonstrates an example of an experimental trial. Each trial consisted of an abstract image being presented in the centre of a projection screen until a response was selected. The participant chose one of the three button-press options. Feedback regarding accuracy of the response (i.e., “Correct” or “Incorrect”) was provided. This provided the basis for learning the stimulus-response associations between each abstract image and the corresponding button-press response.

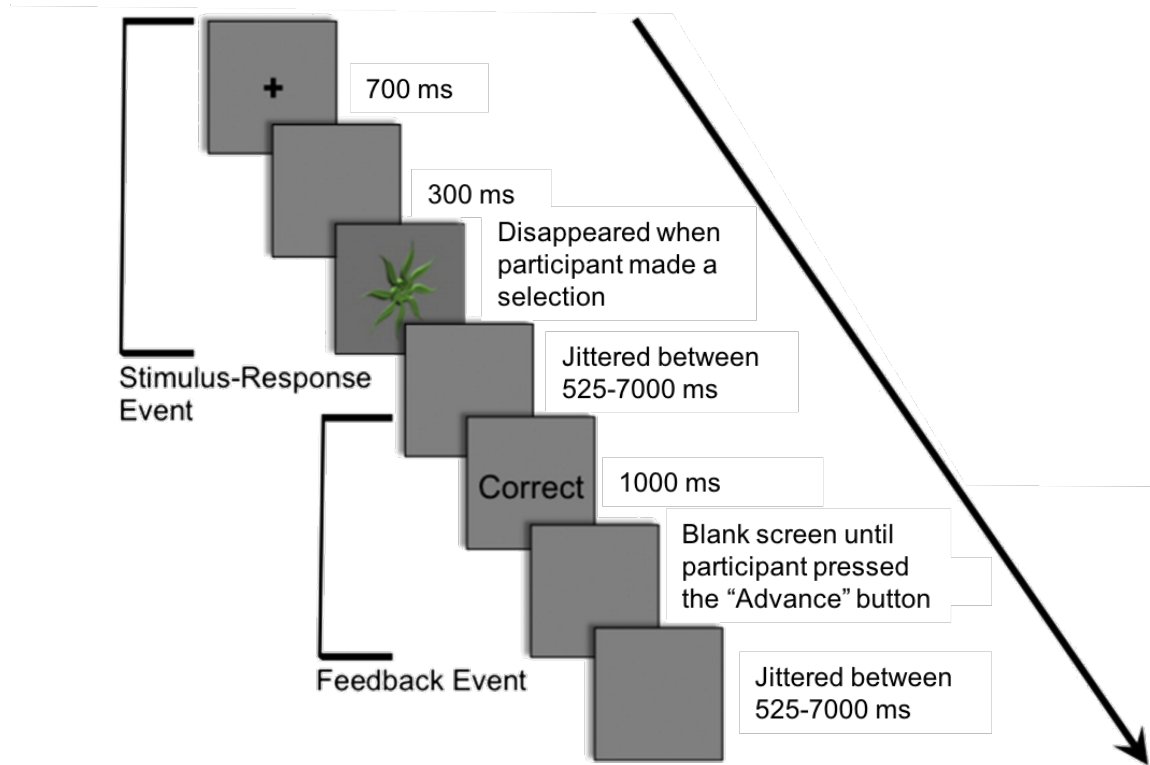


Figure 3.2 Example of a single trial in the experiment.

Participants learned to associate six abstract images with one of three button-press responses in Phase 1. The following is an example of a trial: (i) a cross appeared in the centre of the projection screen for 500 ms; (ii) a blank screen occurred for 500 ms; (iii) an abstract image was presented in the centre of the projection screen until a button-press response; (iv) a blank screen appeared for a variable period of time sampled from an exponential distribution (mean: 2500 ms; minimum: 525 ms; maximum: 7000 ms); (v) feedback (i.e., 'Correct' or 'Incorrect') appeared for 1000 ms; (vi) a blank screen appeared for a variable period of time sampled from an exponential distribution (mean: 2500 ms; minimum: 525 ms; maximum: 7000 ms).

Trials were organized into five blocks. Each block was comprised of 24 trials—with each abstract image randomly appearing twice within each block. After each block, a percentage score was displayed—indicative of their performance.

There were four buttons on the button box. Each of the second, third, and fourth buttons corresponded to four abstract images. Participants pressed these three buttons with their index, middle, and ring fingers, respectively. The first button, pressed by the thumb, served to advance from the feedback phase to the next trial. Therefore, motor responses were included in both decision-making and feedback phases.

Trials proceeded as follows: (i) a cross appeared in the centre of the projection screen for 700 ms; (ii) a blank screen occurred for 300 ms; (iii) an abstract image was presented until a button-press response was made; (iv) a blank screen appeared for a variable period of time; (v) feedback (i.e., “Correct” or “Incorrect”) appeared for 1000 ms; (vi) a blank screen appeared until the participant pressed the first button with his/her thumb to proceed to the next trial; (vii) a blank screen appeared for a variable period of time.

The inter-stimulus interval (ISI), the period between the response selection and feedback, and the inter-trial interval (ITI), the duration between the offset of feedback and the onset of the following trial, were jittered. These intervals varied in duration and the length of time was sampled from an exponential distribution (mean: 2500 ms; minimum: 525 ms; maximum: 7000 ms).

These variable intervals served to distinguish two independent events within each trial: the Stimulus-Response Decision event and the Feedback event (Figure 3.2). As previously discussed, the Stimulus-Response Decision event consisted of exposure to the abstract image until a button-press response was selected. The Feedback or learning event consisted of the duration in which feedback was provided. In addition to distinguishing between Stimulus-Response Decision and Feedback events, Rest events will serve as establishing baseline activity.

3.2.3 Behavioural Data Analysis

In each block, each stimulus was presented twice. Comparing response times (RT) for *accurately-performed* first presentation of stimuli in the final block of the session (i.e., Block 5), with RT for *accurately-performed* second presentations of stimuli in the second to last block of the session (i.e., Block 4), provided our measure of stimulus-response decision performance that was free from new feedback-based learning. Independent t-tests were conducted on Final Block RT Change Scores between OCD patients and Controls.

Response accuracy (%) was recorded for each block and the slope was calculated across all five blocks to operationalize the rate at which participants learned the stimulus-response associations across all five blocks. Block 0 was included in the calculation with a value of zero, as participants are assumed to have no prior learned association between the abstract images and the correct button-press responses. The equation used to calculate slope was the standard slope of the linear regression function (Microsoft Excel, 2017):

$$b = \frac{\sum (x - \bar{x})(y - \bar{y})}{\sum (x - \bar{x})^2}$$

where b is the slope, and x and y are the sample means of the number of blocks and block scores, respectively. Statistical analysis involving an independent unpaired Student's t-Test for slope of learning scores between OCD patients and healthy controls.

3.2.4 Imaging Acquisition

fMRI data were collected in a 3T Siemens Magnetom Prisma with Total Imaging Matrix MRI at Robarts Research Institute at the University of Western Ontario. A scout image was taken to properly orient the participant and T1 for anatomical localization. Five runs of T2*-weighted functional acquisitions were completed, each consisting of one block with 24 trials. Each run lasted approximately 5 minutes. A whole brain image was taken every 2.5 s, each consisting of 43, 2.5 mm-thick slices. The field of view was oriented along the anterior and posterior commissure of the brain with a matrix of 88 x 88 pixels. Each isotropic voxel size was 2.5×2.5×2.5 mm³. The echo time was 30 ms and the flip angle was 90°.

3.2.5 fMRI Data Analysis

Statistical Parametric Mapping version 12 (SPM12; Wellcome Department of Imaging Neuroscience, London, United Kingdom) was used in conjunction with Matrix Laboratory (MATLAB, Mathworks, Inc., Natick, Massachusetts, United States) to complete fMRI analysis. The scans were slice-time corrected, reoriented for participant motion, spatially

normalized to the standard Montreal Neurological Institute (MNI) template, smoothed with an 8 mm full-width, half maximum Gaussian kernel, and high-pass filtered (0.0056 Hz).

Fixed-effect analyses were input into SPM12 to model each participant's data. Regressors were generated by convolving onsets and durations of Stimulus-Response Decision, Feedback, and Rest (i.e., ITI) events with the canonical hemodynamic response function. The Stimulus-Response Decision event was demarcated as the time between onset of abstract image presentation and button-press response, the Feedback event as the time between onset of feedback, lasting 1000 ms, including until the participant pressed the first button to proceed to the next trial. As a result, participant motor response occurred in both Stimulus-Response Decision and Feedback events. A general linear model, or GLM, was created and included the regressors for the Stimulus-Response Decision, Feedback, and Rest events. The GLM examined regional blood-oxygenation-level dependent (BOLD) activity associated with these events. A second GLM was created modelling only Rest events, both ISI and ITI events to investigate baseline activity. Several studies investigating baseline activity in patients with OCD have found hypoactive DS and hyperactive VS compared to controls. The Rest events here were modelled to investigate this further and determine if baseline activity correlated with behavioural or clinical measures, including YBOCS.

The Harvard-Oxford Subcortical Atlas in the FMRIB Software Library version 5.0 (FSL v5.0; Analysis Group, FMRIB, Oxford, United Kingdom) was used to define striatal regions. MNI space was used as an x , y , and z coordinate system to delineate each region. The VS was defined as $z < 2$ in MNI space, including the nucleus accumbens and the ventral portion of the caudate nucleus and putamen (Postuma & Dagher, 2006). The DS was defined as $z \geq 2$ in MNI space, consisting of the bulk of the caudate nucleus and putamen (Postuma & Dagher, 2006).

Contrast models were created to examine differences in VS and DS activity, as well as in other brain regions, between the OCD and control groups during different events in the stimulus-response task. The following contrasts of interest were analyzed: (i) Stimulus-Response Decision events minus Rest (i.e., ITI interval) collapsed across Group (OCD and

control); (ii) Feedback events minus Rest collapsed across Group (OCD and control); (iii) Stimulus-Response Decision events for the OCD group minus for the control group; (iv) Feedback events for the OCD group minus for the control group; (v) Rest events for OCD minus for control; and (vi) Rest events for control minus for OCD Rest events. Contrast images were examined at the group level in SPM12 for Stimulus-Response Decision, Feedback, and Rest events in a separate model. A secondary analysis was performed correlating behavioural and clinical data analysis with BOLD analysis during Stimulus-Response Decision, and Feedback events for the OCD and control groups.

3.2.6 Correlation Analysis

Next, we investigated brain-behaviour correlations to confirm that behavioural performance was related to DS versus VS activity patterns. We tested whether BOLD signal in striatal regions correlated with behavioural indices of response selection decisions and learning respectively. Specifically, we tested whether activity in two anatomical DS ROIs consisting of regions of the caudate nucleus and putamen above $z=2$, and two VS ROIs, consisting of the NAcc and regions of the caudate nucleus and putamen ventral to $z=2$ were correlated with Final Block RT Change (i.e., our measure of response-selection decisions), and with Learning Slope (i.e., our measure of learning efficiency). Correlations were performed separately for OCD and healthy control groups in the event that learning and response selection performance differed across groups. The two DS and VS ROIs were employed for the correlation analysis in the present study using the MarsBar Toolbox in SPM12 (Brett, Anton, Valabregue, & Poline, 2002). Beta values in our ROIs were extracted from four contrasts of interest: (i) Stimulus-Response Decision Events minus Rest for patients with OCD; (ii) Feedback Events minus Rest for patients with OCD; (iii) Stimulus-Response Decision Events minus Rest for healthy controls; and (iv) Feedback Events minus Rest for healthy controls. These average beta values for each ROI were correlated with behavioural measures of stimulus-specific response selection (i.e., the Final Block RT Change) and learning (i.e., Learning Slope) for each group separately.

Additionally, beta values were extracted for OCD patients from the rest model and the experimental model described above to investigate whether baseline activity levels

correlated with OCD symptoms. Specifically, the two DS and VS ROIs were correlated with YBOCS-total, YBOCS-obsession, and YBOCS-compulsion scores, independently.

3.3 Results

3.3.1 Behavioural data

Demographic, affective, cognitive, and clinical data are presented in Table 3.1 and behavioural data are presented in Table 3.2.

3.3.1.1 Demographic, affective, cognitive, and clinical data

The mean (SEM) ages of the patient and control groups were 26.07 (1.65) and 24.50 (0.68), respectively. The mean (SEM) education levels of the patient and control groups were 16.93 (0.66) and 17.55 (0.45), respectively. There were no significant demographic differences between OCD and control participants (Table 3.1) in demographic or cognitive data. Participants with OCD scored significantly higher on Beck Depression Inventory II, Beck Anxiety Inventory, and Oxford Happiness Questionnaire compared to controls, as would be expected given the nature of OCD. YBOCS was administered to OCD patients only. Again the YBOCS measures the presence and severity of obsessive compulsive symptoms. The scale yields a total score as well as a sub-score for obsessions and compulsions, although only the total score is interpreted clinically. The current OCD cohort had a mean total score of 18 which suggests moderately severe OCD (Goodman, Price, & Rasmussen, 1989). YBOCS total scores ranged from 8 (mild OCD) to 26 (severe OCD), suggesting a wide range OCD severity (Goodman et al., 1989).

Table 3.1 Health and demographic information for participants in the OCD and control groups.

	OCD	Control	<i>p</i> value
Number of participants	14	16	–
Age	26.07 (1.65)	24.50 (0.68)	0.39
Education level	16.92 (0.65)	17.54 (0.45)	0.48
YBOCS – Total Score	18.00 (1.59)	–	–

YBOCS–Obsession sub-score	9.71 (0.85)	–	–
YBOCS–Compulsion sub-score	8.29 (1.08)	–	–
BDI-II	11.64 (2.54)	4.00 (0.95)	0.01*
BAI	9.14 (1.44)	3.00 (0.89)	0.002*
SAS	9.86 (1.25)	8.91 (0.96)	0.58
ANART	121.67 (1.85)	120.88 (1.45)	0.76
Epworth Sleepiness Scale	8.21 (1.30)	5.54 (0.67)	0.10
Oxford Happiness score	3.79 (0.17)	5.08 (0.14)	0.00002*
BIS-11	58.36 (2.64)	56.54 (3.75)	0.73
MoCA	27.86 (0.49)	28.82 (0.40)	0.17

Values are presented as group means and standard error of the mean (SEM) in braces. ANART – National Adult Reading Test IQ Estimation; MOCA – Montreal Cognitive Assessment total score out of 30; BDI-II– Beck Depression Inventory II; BAI – Beck Anxiety Inventory; BIS-11 – Barratt Impulsiveness Scale; SAS – Starkstein Apathy Scale; YBOCS – Yale-Brown Obsessive Compulsive Scale. *indicates statistical significance ($p < 0.05$).

3.3.1.2 Measure of Decision making efficiency

Stimulus-response decision making was assessed using a difference score between the mean RT of the first presentation of each of the stimuli that were associated with correct responses of Block 5 and the mean RT of the second presentation of each of the stimuli that were associated with correct responses of Block 4. As the participant progresses through the blocks, associations become better learned and decision making requires less and less deliberation, measured by progressively shorter RTs across blocks. Consequently, intact decision making should result in a *negative* Final Block RT Change Score because the mean RT in the first presentation of Block 5 should be faster than the mean RT in the second presentation of Block 4. We found significantly less improvement in Block 5 RT relative to Block 4 RT for OCD patients compared to controls ($t=1.90$, $p=0.033$; Figure 3.3A). In fact, the score was positive for OCD patients, meaning that they slowed down in Block 5 relative to Block 4, whereas controls had the expected speeding up of RT, characteristic of a decision that required lesser deliberation.

It is important to note that mean RT and accuracy in the final block did not differ significantly between OCD patients and controls (Final Block Mean RT: $t=0.53$, $p=0.701$; Final Block Mean Accuracy: $t=0.76$, $p=0.226$).

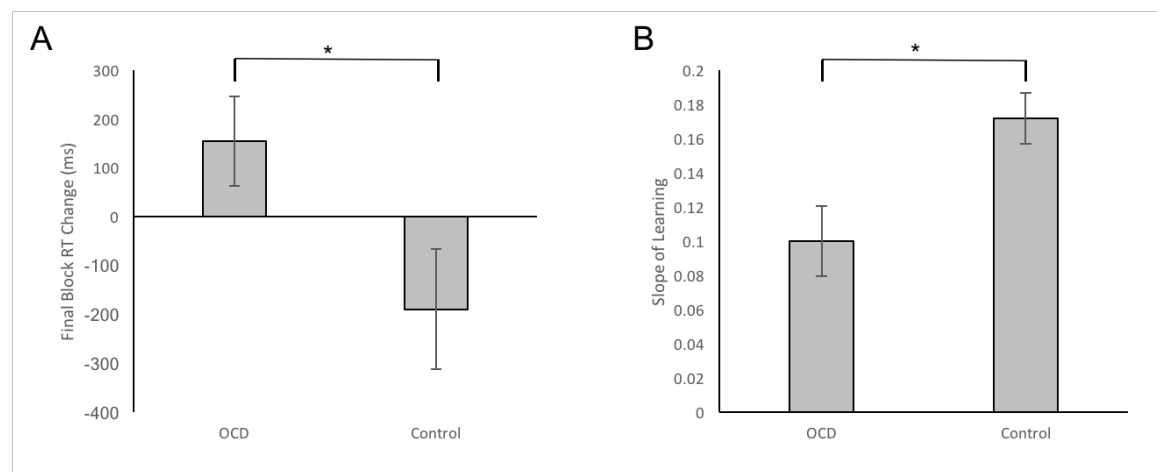
Table 3.2 Behavioural measures for patients with OCD and control participants.

	Final Block Accuracy (%)	Final Block Mean RT (ms)	Final Block RT Change (ms)	Slope of Learning
OCD	76.20 (5.74)	1316.72 (138.10)	153.74 (91.87)	0.085 (0.015)
Control	84.72 (3.72)	1251.05 (97.84)	-190.06 (123.16)	0.132 (0.016)

Values are presented as group means and SEM in braces. Final Block RT Change is a difference score between the mean RT of the first presentation of each of the stimuli that were associated with correct responses of Block 5 and the mean RT of the second presentation of each of the stimuli that were associated with correct responses of Block 4. Slope of Learning was calculated using the linear regression function in Microsoft Excel (2011).

3.3.1.3 Measure of stimulus-response association learning

Efficiency of stimulus-response association learning was estimated using the slope of accuracy change over five blocks of stimulus-response trials. Slope was calculated using the linear regression function in Microsoft Excel (2011). An independent sample t-test on slopes of learning was conducted between OCD and control participants. We found significantly *slower* learning in patients with OCD compared to control participants ($t=2.53$, $p=0.008$; Figure 3.3B).

**Figure 3.3 Behavioural Data in Patients with OCD and Healthy Controls.**

A) Final Block RT Change was our measure of decision making efficiency. It was calculated by subtracting the mean RT for correct events of the first presentation of the stimuli in Block 5 from the mean RT for correct

evens of the second presentation of the stimuli in Block 4. We found significantly less improvement in Block 5 RT relative to Block 4 RT for OCD patients compared to controls ($t=1.90$, $p=0.033$; Figure 3.3A). **B)** Slope of learning served as a measurement of learning efficiency. To reiterate, slope was calculated using the block accuracy scores over five blocks using the slope of the linear regression function (Microsoft Excel 2011). Slope of learning was significantly slower in OCD patients compared to healthy controls. Error bars represent standard error of the mean. * $p<0.05$.

3.3.2 FMRI data

Significant activations in contrasts of interest are presented in Tables 3.3-5 and Figures 3.4-6. Contrasts are reported at a significance level of $p<0.05$ FWE, unless otherwise indicated.

3.3.2.1 Groups collapsed

Stimulus-Response Decision events: Significant activity arose in the right dorsal caudate in the Stimulus-Response Decision relative to Rest contrast (*peak coordinates:* 12, 5, 2; $t=4.55$, $p=0.030$ FWE).

Feedback learning events: Significant activity in the VS arose in the left ventral putamen in the Feedback Events minus Rest contrast (*peak coordinates:* -30, -7, -1; $t=4.42$, $p=0.048$ FWE).

Table 3.3 Significant brain activations in contrasts of interest collapsed across Group (OCD and control) reported in MNI space.

Contrast	Anatomical Area	Cluster Size	t	p_{FWE}	x, y, z
SR minus Rest	Right Dorsal Caudate	2	4.55	0.030	12, 5, 2
	Left Inferior Temporal Gyrus	1	5.13	0.003	-48, -55, -13
	Left Insula	2	5.11	0.003	-30, 20, -4
	Right Insula	2	5.05	0.004	30, 23, -1
	Right Primary Visual Cortex	2	4.89	0.007	6, -82, -4
	Right Lateral Occipital Complex	1	4.63	0.021	51, -49, -13
	Left Middle Frontal Gyrus	1	4.53	0.032	-33, 53, -1
	Left Postcentral Gyrus	1	4.52	0.033	-45, -28, 38
FB minus Rest	Left Ventral Putamen	1	4.42	0.048	-30, -7, -1
	Right Cerebellum	31	5.52	<0.001	12, -49, -16

Left Thalamus	1	4.72	0.015	-15, -7, 8
Left Temporal Occipital				
Fusiform Cortex	1	4.68	0.018	-39, -58, -10
Right Pons	1	4.56	0.028	9, -31, -22
Right Midbrain	1	4.56	0.028	6, -28, -19

Cluster size is reported in voxels. Coordinates are reported in MNI space. Striatal regions are presented first and highlighted in each contrast. N.B. SR – Stimulus-Response Decision Events; FB – Feedback Events.

3.3.2.2 OCD versus healthy controls

Stimulus-Response Decision events: Control minus OCD. Significant activity occurred in the bilateral dorsal caudate nuclei (*peak coordinates: 15, 2, 14; $t=5.32$, $p=0.001$ FWE, and peak coordinates: -12, -1, 8; $t=4.64$, $p=0.019$ FWE; Figure 3.5A) in the control minus OCD Stimulus-Response Decision events.*

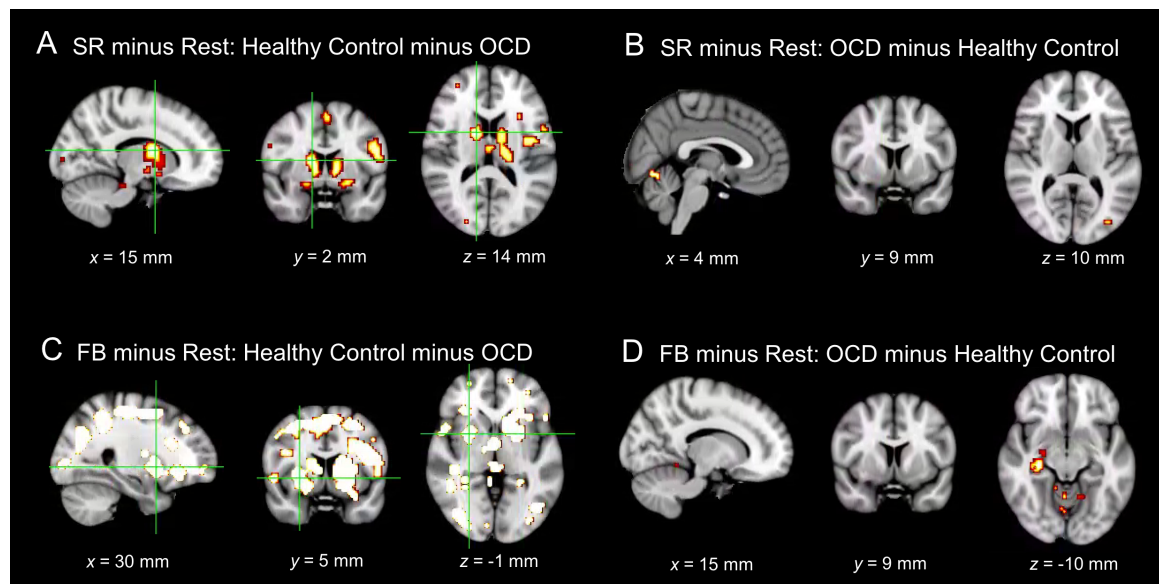


Figure 3.4 Significant activations in contrasts of interest comparing healthy controls and patients with OCD.

Activation maps are presented at a threshold of $p < 0.001$ uncorrected for multiple comparisons to allow for visualization of activation in all contrasts. **A)** BOLD signal for healthy control minus OCD patients for Stimulus-Response Decision Events minus Rest. Significant activity occurred in the bilateral dorsal caudate nuclei (peak coordinates: 15, 2, 14; $t=5.32$, $p=0.001$ FWE, and peak coordinates: -12, -1, 8; $t=4.64$, $p=0.019$ FWE). **B)** BOLD signal for OCD patients minus healthy controls for Stimulus-Response Decision Events minus Rest. No significant activity arose in the striatum. **C)** BOLD signal for healthy controls minus OCD patients for

Feedback Events minus Rest. Significant activity arose in bilateral ventral putamina (peak coordinates: 30, 5, -1; $t=5.61$, $p<0.001$ FWE, and peak coordinates: -27, 2, -1; $t=5.05$, $p=0.004$ FWE), as well as left dorsal putamen (peak coordinates: -27, -1, 11; $t=5.67$, $p<0.001$ FWE). **D)** BOLD signal for OCD patients minus healthy controls for Feedback Events minus Rest. No significant activity arose in the striatum. N.B. SR – Stimulus-Response Decision Events and FB – Feedback Events in the figure.

Stimulus-Response Decision events: OCD minus control. No activity occurred in the striatum at $p<0.05$ FWE, or even at the liberal threshold of $p<0.001$ uncorrected when OCD Stimulus-Response Decision events were contrasted with control events (Figure 3.5B).

Feedback events: control minus OCD. Significant activity arose in bilateral ventral putamina (peak coordinates: 30, 5, -1; $t=5.61$, $p<0.001$ FWE, and peak coordinates: -27, 2, -1; $t=5.05$, $p=0.004$ FWE), as well as left dorsal putamen (peak coordinates: -27, -1, 11; $t=5.67$, $p<0.001$ FWE) in the control minus OCD Feedback events contrast (Figure 3.5C).

Feedback events: OCD minus control. No activity occurred in the striatum at $p<0.05$ FWE, or even at the liberal threshold of $p<0.001$ uncorrected in the OCD minus control Feedback events contrast (Figure 3.5D).

Table 3.4 Significant brain activations in patients with OCD versus healthy controls in contrasts of interest reported in MNI space.

Contrast	Anatomical Area	Cluster Size	t	p_{FWE}	x, y, z
<u>SR Events</u>					
OCD minus control	Left Lateral Occipital Cortex	5	3.98	$<0.001^*$	-36, -82, 8
	Right Cerebellum	16	3.97	$<0.001^*$	3, -70, -10
	Left Cerebellum	11	3.62	$<0.001^*$	-18, -52, -16
Control minus OCD	Right Dorsal Caudate	21	5.32	0.001	15, 2, 14
	Left Dorsal Caudate	8	4.64	0.019	-12, -1, 8
	Left Insular Cortex	48	6.33	<0.001	-30, 26, 5
	Right Insular Cortex	19	5.26	0.001	33, 26, 2
	Right Frontal Orbital Cortex	9	4.97	0.005	42, 20, -7
	Left Precentral Gyrus	9	4.93	0.006	-54, 5, 22
	Right Middle Frontal Gyrus	1	4.57	0.025	51, 23, 29

FB Events						
OCD	minus					
control		Right Cerebellum	52	4.56	<0.001*	12, -46, -19
		Right Angular gyrus	49	4.18	<0.001*	48, -46, 26
		Right Hippocampus	22	4.17	<0.001*	33, -25, -10
		Right Middle Temporal gyrus	35	4.04	<0.001*	63, -43, 2
		Left Lateral Occipital Cortex	35	3.69	<0.001*	-48, -67, 8
		Right Occipital Fusiform gyrus	6	3.67	<0.001*	39, -58, -7
		Left Cerebellum	7	3.55	<0.001*	-15, -55, -16
		Left Inferior Temporal gyrus	7	3.40	<0.001*	-39, -58, -1
		Right Supramarginal gyrus	1	3.18	0.001*	51, -22, 32
		Right Amygdala	1	3.16	0.001*	27, -10, -13
		Right Inferior Temporal gyrus	1	3.15	0.001*	51, -19, -22
		Left Superior Temporal gyrus	1	3.13	0.001*	-60, -22, -4
Control	minus					
		OCD				
		Right Ventral Putamen	28	5.61	<0.001	30, 5, -1
		Left Ventral Putamen	**	5.05	0.004	-27, 2, -1
		Left Dorsal Putamen	113	5.67	<0.001	-27, -1, 11
		Left Lateral Occipital Cortex	56	5.81	<0.001	-42, -70, -4
		Right Lateral Occipital Cortex	5	5.17	0.002	-27, 5, 29
		Right Occipital Pole	5	5.13	0.002	27, -91, -1
		Left Postcentral gyrus	7	4.79	0.011	-57, -19, 26
		Left Supramarginal gyrus	8	4.77	0.012	-51, -31, 47
		Left Inferior Frontal gyrus	2	4.73	0.014	-54, 11, 5
		Left Inferior Temporal gyrus	2	4.67	0.018	-45, -49, -16
		Left Supplementary Motor Cortex	7	4.66	0.018	-3, 2, 56
		Right Inferior Temporal gyrus	2	4.50	0.034	45, -49, -13

Cluster size is reported in voxels. Coordinates are reported in MNI space. Striatal regions are presented first and highlighted in each contrast. *Indicates a threshold of $p < 0.001$ uncorrected. **Cluster size unobtainable as peak coordinates are within a larger cluster. N.B. SR – Stimulus-Response Decision Events; FB – Feedback Events.

3.3.2.3 Rest-Only Model

Rest events control minus OCD: No activity in the striatum arose for the control minus OCD Rest events contrast.

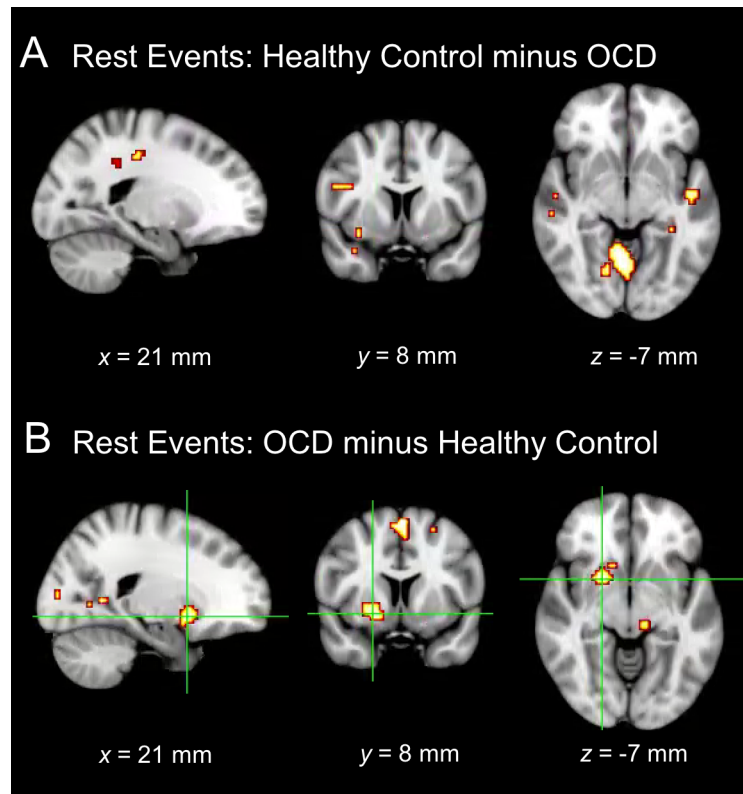


Figure 3.4 Significant activations in contrasts of interest involving Rest Events.

Activation maps are presented at a threshold of $p < 0.001$ uncorrected for multiple comparisons to allow for visualization of activation in all contrasts. **A)** BOLD signal for healthy control minus OCD patients for Rest Events. No activity arose in the striatum. **B)** BOLD signal for OCD patients minus healthy controls for Rest Events. Significant activity arose in the right ventral putamen (peak coordinates: 21, 8, -7; $t = 3.62$, $p = 0.001$).

Rest events OCD minus control: No activity occurred at a threshold of $p < 0.05$ FWE, but at the more liberal threshold of $p < 0.001$ uncorrected, activity arose in the right ventral putamen (peak coordinates: 21, 8, -7; $t = 3.62$, $p = 0.001$).

Table 3.5 Significant brain activations during Rest events in patients with OCD versus healthy controls in contrasts of interest reported in MNI space.

Contrast	Anatomical Area	Cluster Size	<i>t</i>	<i>p</i> _{FWE}	<i>x, y, z</i>
<u>Rest events</u>					
OCD minus control	Right Ventral Putamen	47	3.62	0.001*	21, 8, -7
	Left Central Operculum Cortex	54	4.85	<0.001*	-57, -4, 11
	Superior Frontal Gyrus	119	3.60	0.001*	0, 11, 62
	Right Central Operculum Cortex	46	3.38	0.001*	48, -10, 14
Control minus OCD	No suprathreshold activations				

Cluster size is reported in voxels. Coordinates are reported in MNI space. Striatal regions are presented first and highlighted in each contrast. *Indicates a threshold of $p < 0.001$ uncorrected. N.B. SR – Stimulus-Response Decision Events; FB – Feedback Events.

3.3.2.4 Brain-behaviour Correlations: OCD and controls separately

One right and left ROI encompassing the entirety of the VS and one right and left DS ROI encompassing the entirety of the DS were employed. Beta values for the four ROIs were extracted separately from Stimulus-Response Decision events, Feedback events, and Rest events. BOLD signal in these ROIs was correlated with behavioural measures for OCD patients and controls separately. We expected that baseline DS and VS neural activity might correlate with disease severity given previous findings of DS hypoactivity and VS hyperactivity in OCD. Therefore, we correlated measures of disease severity with beta values extracted from DS and VS ROIs. Specifically, YBOCS total score and YBOCS sub-scores of OCD patients were correlated with BOLD signal in these ROIs with beta values extracted from the Rest-only model.

3.3.2.4.1 Striatum and decision making efficiency

Final Block RT Change scores were correlated with beta values from each of the two DS and VS ROIs, separately for OCD patients and healthy controls. For control participants a significantly negative correlation occurred between Final Block RT Change and beta

values in the left DS ROI during Stimulus-response Decision Events minus Rest ($r=-0.552$, $t=1.99$, $p=0.033$; Figure 3.7A), suggesting that those participants with greater activity in the left DS had quicker RTs in the first stimulus presentation in Block 5 compared to the second stimulus presentation in Block 4. No significant correlation arose in control participants for our decision-making efficiency score and BOLD signal during Feedback Events minus Rest. For OCD patients our decision-making efficiency score did not correlate with neural activity during Stimulus-Response Decision or Feedback Events minus Rest.

3.3.2.4.2 Striatum and learning from feedback

Learning slope was correlated with beta values from each of the VS and DS ROIs, separately for OCD patients and controls. Looking at the control data, a significant, positive correlation occurred between slope of learning and Feedback Event minus Rest beta values extracted from the left VS ROI ($r=0.542$, $t=1.93$, $p=0.037$; Figure 3.7B). No significant or trending correlations were present in the control participants' data relating slope and BOLD signal during Stimulus-response Decision Events. For OCD patients, learning slope, our measure of learning efficiency, did not correlate with neural activity during either Feedback or Stimulus-Response Decision Events minus Rest.

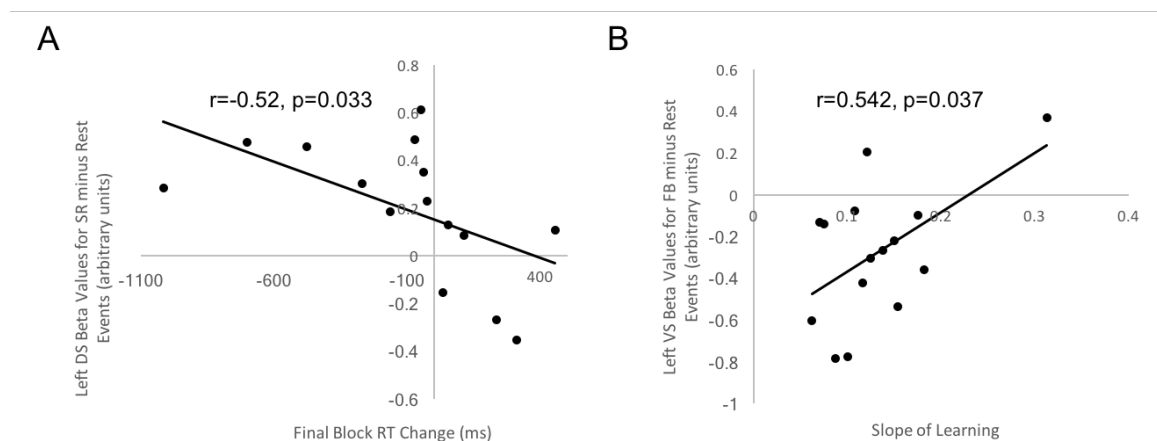


Figure 3.5 Correlation between behavioural indices of decision making and learning for control participants and beta values in striatal ROIs.

A) Correlation between Final Block RT Change and beta values in left DS ROI in healthy controls ($r=-0.552$, $t=1.99$, $p=0.033$). **B)** Correlation between Learning Slope and beta values of left VS ROI in healthy controls. Beta values were significantly, positively correlated with slope of learning ($r=0.542$, $t=1.93$, $p=0.037$).

3.3.2.4.3 Striatum and severity of OCD

Compulsion sub-score of the YBOCS significantly, negatively correlated with beta values in both the left and right VS ROIs (Left VS ROI: $r=-0.565$, $t=2.47$, $p=0.035$, Figure 3.8A; Right VS ROI: $r=-0.604$, $t=2.73$, $p=0.022$, Figure 3.8B). YBOCS total score trended towards being negatively correlated with Left VS ($r=-0.470$, $t=1.42$, $p=0.090$) and Right VS ROIs ($r=-0.493$, $t=1.55$, $p=0.073$). Obsession sub-scores did not correlate with beta values in either Left VS ($r=-0.160$, $t=0.22$, $p=0.584$) and Right VS ROIs ($r=-0.152$, $t=0.27$, $p=0.604$). OCD disease severity did not significantly correlate with either Left or Right DS ROIs (Left DS ROI: Total YBOCS $r=-0.046$, $t=0.16$, $p=0.876$, Obsession sub-score $r=0.085$, $t=0.30$, $p=0.773$, Compulsion sub-score $r=-0.134$, $t=0.47$, $p=0.647$; Right DS ROI: Total YBOCS $r=-0.164$, $t=0.58$, $p=0.575$, Obsession sub-score $r=-0.011$, $t=0.04$, $p=0.971$, Compulsion sub-score $r=-0.233$, $t=0.83$, $p=0.424$).

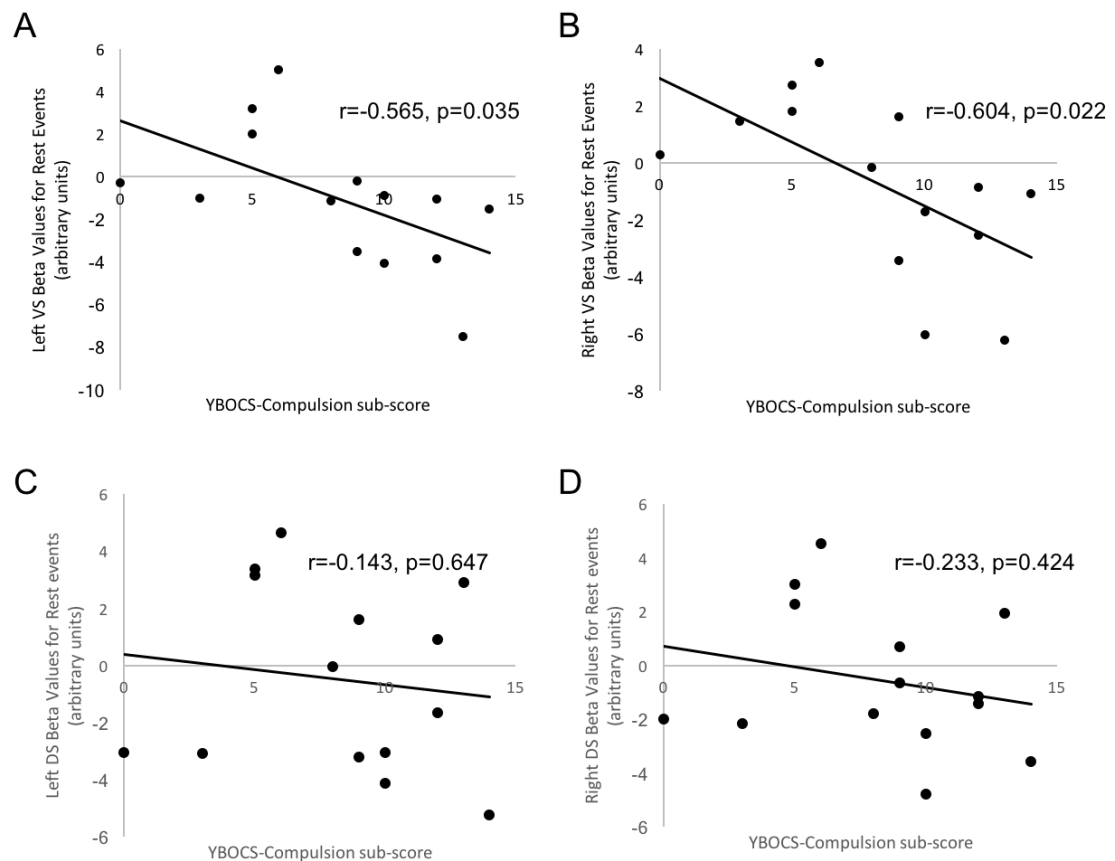


Figure 3.6 Correlation between DS and VS ROIs and YBOCS-compulsion sub-scores in patients with OCD.

A) Correlation between YBOCS-Compulsion sub-score and beta values of left VS ROI in patients with OCD. Beta values significantly, negatively correlated with YBOCS-Compulsion sub-score ($r = -0.565$, $p = 0.035$). **B)** Correlation between YBOCS-Compulsion sub-score and beta values of right VS ROI in patients with OCD. Similarly, beta values significantly, negatively correlated with YBOCS-Compulsion sub-score ($r = -0.604$, $p = 0.022$). **C)** Correlation between YBOCS-Compulsion sub-score and beta values of left DS ROI in patients with OCD ($r = -0.143$, $p = 0.647$). **D)** Correlation between YBOCS-Compulsion sub-score and beta values of right DS ROI in patients with OCD ($r = -0.233$, $p = 0.424$). No significant correlations arose comparing YBOCS-Compulsion sub-score and DS ROIs in patients with OCD.

3.4 Discussion

In the current investigation, OCD patients responded slower on the first presentation of stimuli in the final block compared to the second stimuli presentation in the previous block, compared to healthy controls who responded faster. This is evidence for poorer decision making in OCD patients compared to controls. Additionally, we found that patients with OCD learned the stimulus-response associations significantly slower compared to healthy controls based on slope of learning.

Activity in DS correlated with Stimulus-Response Decision Events and *not* with Feedback events, when stimulus-response associations are actually learned, in OCD patients and controls participants combined. We also found that Final Block RT Change score (i.e. our measure of decision making efficiency) negatively correlated with beta values in the left DS ROI in healthy controls. Learning Slope (i.e. our measure of learning) did not correlate with beta values in DS in controls or in patients with OCD. These results support a role for DS in decision making and not learning, confirming our results in Nole M. Hiebert, Vo, et al. (2014) and in Chapter 2.

In contrast, VS was recruited during Feedback Events for OCD patients and controls combined. To reiterate, the Feedback event is when deterministic feedback is received and learning takes place. Further, Learning Slope correlated significantly with beta values in the left VS of healthy controls. These findings support the notion that VS mediates stimulus-response learning.

These distinct cognitive roles for DS and VS were investigated in OCD patients relative to healthy controls. Patients with OCD evidenced less efficient decision-making, with greater deliberation and no speeding up of response selection decisions from Block 4 to the final block of the experiment, relative to controls who showed significant reductions in RTs. This was despite equal accuracy between controls and patients with OCD. Consistent with these behavioural findings, DS was more strongly recruited during Stimulus-Response Decision Events for controls compared to patients with OCD. Patients with OCD also showed diminished learning, with a lower slope of stimulus-response association learning

across blocks, compared to healthy controls. In keeping with this, VS activity was greater during Feedback Events in healthy controls compared to OCD patients. OCD patients did not evidence any significant correlations between our measures of decision-making versus learning efficiency and DS or VS BOLD signal. These results strongly suggest diminished decision making and learning in patients with OCD, related to deficits in task-relevant DS and VS activation.

We investigated VS and DS signal in Rest Events in OCD patients and controls. Compared to healthy controls, OCD patients evidenced significantly increased VS activity during Rest Events (i.e., not related to a specific task). Baseline DS activity did not differ between healthy controls and OCD patients. Further, we found that the compulsion sub-score of the YBOCS negatively correlated with VS beta values extracted from Rest, suggesting that this enhanced baseline VS activity was related to disease severity. Total YBOCS and obsession and compulsion sub-score measures did not correlate with DS activity in patients with OCD.

3.4.1 Cognitive functions mediated by the striatum

We independently assessed decision making and stimulus-response learning, using behavioural measures and distinct fMRI events. We aimed to disentangle neural substrates specifically mediating these different cognitive processes.

Our results are contrary to the large literature attributing feedback-based learning to DS (Balleine, Liljeholm, & Ostlund, 2009; Hart, Leung, & Balleine, 2013; Yin & Knowlton, 2006). A potential explanation for the long-standing association of DS with stimulus-response association learning, despite increasing numbers of contradictory results (Atallah et al., 2007; Grahn, Parkinson, & Owen, 2008; Ohira et al., 2010; Reiss et al., 2005), relates to the common confounding of learning and decision-making processes (Jessup & O'Doherty, 2011; McDonald & Hong, 2004). In behavioural studies, learning is generally measured by the accuracy of stimulus-specific response selections that are provided as evidence that learning has occurred. Poor performance therefore could be the result of failing either to learn stimulus-response associations or to correctly select responses based on these learned associations. In fMRI studies, a) enacting a response when presented with

a stimulus, and b) learning from feedback, are typically treated as a single event with all significantly-activated brain regions ascribed a role in learning *per se* (Dobryakova & Tricomi, 2013; Jessup & O'Doherty, 2011; Poldrack et al., 1999). By separately assessing response-selection decisions and learning, our approach aimed to resolve the discrepancy between studies that involve DS in feedback-based learning (Boettiger & D'Esposito, 2005; O'Doherty et al., 2004) versus those in PD patients (Swainson et al., 2000; Vo et al., 2014), and participants with DS lesions (Ell, Marchant, & Ivry, 2006; Exner et al., 2002) that dispute the notion that DS mediates stimulus-response learning.

Our findings integrate with a growing literature favouring a role for DS in decision making rather than learning *per se*. In neuroimaging studies, DS activity consistently remains significantly increased above baseline *after* sequences (Reiss et al., 2005), categorization rules (Helie, Roeder, & Ashby, 2010; Seger, Peterson, Cincotta, Lopez-Paniagua, & Anderson, 2010), stimulus–reward (Daw & Doya, 2006; Seger et al., 2010), and response–reward associations (Ohira et al., 2010) are well-learned. Additionally, DS frequently correlates with response selections, particularly when an element of deliberation is required (N. M. Hiebert, Owen, Seergobin, & MacDonald, 2017), even in contexts *devoid of new learning* (Grahn et al., 2008), such as in the Stroop task (Ali et al., 2010), and in making numeric magnitude judgments (P. A. MacDonald et al., 2011). This activation profile is inconsistent with a brain region mediating learning *per se* and is more in line with one that underlies decisions.

Our results, in contrast suggest that VS mediates learning stimulus-response associations. Replicating our previous findings (Nole M. Hiebert, Vo, et al., 2014), VS signal occurred specifically during the Feedback Event and correlated with efficiency of learning assessed with slope measure in healthy controls. This result fits with the larger literature implicating VS in forms of implicit learning, such as reward (Camara, Rodriguez-Fornells, & Munte, 2010), stimulus-stimulus (P. A. MacDonald et al., 2011), sequence (Ghilardi et al., 2007), motor sequence (Feigin et al., 2003), and category learning (Shohamy, Myers, Geghman, Sage, & Gluck, 2006).

3.4.2 OCD and the striatum

Structural and functional changes within the striatum in patients with OCD could be linked to cognitive dysfunction as well as OCD symptomatology. Deficits in DS and VS could lead to dysfunction in decision making, cognitive flexibility, and reward processing and learning respectively.

Here, OCD patients evidenced poorer decision making coupled with decreased DS activity compared to controls during decision events assessed with fMRI. These results align with the larger literature showing that patients with OCD have diminished DS function in tasks examining cognitive flexibility (Del Casale et al., 2011; Vriend et al., 2013), and response inhibition (Del Casale et al., 2011; van Velzen, Vriend, de Wit, & van den Heuvel, 2014). As cognitive flexibility and response inhibition appear to be reduced in OCD patients, this may be linked to the inability to choose naturally rewarding behaviours over compulsive actions (Vriend et al., 2013). DS deficits in patients with OCD could underlie the poorer cognitive flexibility and deficient response inhibition that lead to compulsive actions.

In the current study, learning was also poorer in patients with OCD related to decreased VS activity during learning events assessed with fMRI. Other studies have shown diminished reversal learning (Remijnse, Nielen, van Balkom, & et al., 2006) and reward learning (Nielen, den Boer, & Smid, 2009) in OCD patients compared to healthy controls. Remijnse et al. (2006), ascribe impairments in task-switching and learning to striatal deficiencies, which they purport as significant contributors to the neurological foundations of ineffective behavioural adaptation to changing stimuli and cognitive inflexibility in OCD patients. Compulsive behaviours are the manifestations of such neural impairments. Obsessive-compulsive behaviours have been linked to hyperactivity in the VS at baseline (Baxter et al., 1987; de Vries et al., 2017; Del Casale et al., 2011; Figeet et al., 2011; Gursel, Avram, Sorg, Brandl, & Koch, 2018; Le Jeune et al., 2010; Perani et al., 1995; Rauch, 1997). Augmented baseline VS activity in patients with OCD impairs performance on VS-mediated tasks and may play an integral role in OCD symptomatology.

A present model of OCD based on data discussed above suggests that obsessions and compulsive behaviours might be linked to a disproportion between hyperactivity in the VS

and hypoactivity in the DS while processing incoming information. Dysfunctional reward circuitry centred in the VS results in an inability to respond to natural rewards and instead VS activation is modulated by stressful, obsession-related stimuli (Baxter et al., 1987; de Vries et al., 2017; Del Casale et al., 2011; Figee et al., 2011; Gursel et al., 2018; Le Jeune et al., 2010; Perani et al., 1995; Rauch, 1997). Concurrent, hypoactivity in DS results in deficits in cognitive flexibility and response inhibition. These impairments are related to difficulty switching away from thinking of obsessions, and toward performing adaptive actions over maladaptive compulsions (Del Casale et al., 2011; van Velzen et al., 2014; Vriend et al., 2013). Our results are entirely supportive of these models. Further, we found a strong negative association between between compulsion sub-score on the YBOCS and bilateral beta values in VS ROIs at baseline. This suggests that patients with high baseline VS activity, relative to other OCD patients, do not rate compulsive behaviours highly in their OCD phenotype. There is evidence to suggest the reward system in OCD patients is hijacked to regard OCD behaviours as rewarding, rather than natural rewards (i.e. food, sex; Del Casale et al., 2011; Figee et al., 2011; Remijnse et al., 2006). This could be explained by reports of hyperactive VS (i.e. integral structure in the reward system) at rest (de Vries et al., 2017) and in response to symptom-provoking stimuli (Rauch et al., 1994), compared to natural rewards, relative to controls (Remijnse et al., 2006). Patients with exceptionally hyperactive VS at rest, compared to other patients with OCD, may not even respond to OCD-related compulsive behaviours as rewarding and therefore these patients may not perform them, or do not feel they are significant burdens in their OCD, as our data suggests.

3.4.3 Conclusions

Our findings dispute the prevalent notion that DS mediates stimulus-response learning. We showed that DS mediates response selections whereas VS underlies feedback-based learning in PD patients and healthy age-matched controls. This study provides strong support for the cognitive deficits that arise in OCD that might sustain compulsive behaviour and obsessive thinking. Further, these cognitive deficits seem to implicate DS and VS respectively. Finally, baseline VS hyperactivity relates to lower compulsions. We ascribe

this to a decreased ability of VS to signal rewards due to its persistent elevated state, even those rewards that arise due to performance of compulsions and temporary relief of anxiety.

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Chapter 4

4 Dorsal striatum mediates deliberate decision making, not late-stage, stimulus-response learning

We investigated a controversy regarding the role of the dorsal striatum (DS) in deliberate decision-making versus late-stage, stimulus–response learning to the point of automatization. Participants learned to associate abstract images with right or left button presses explicitly before strengthening these associations through stimulus–response trials with (i.e., Session 1) and without (i.e., Session 2) feedback. In Session 1, trials were divided into response-selection and feedback events to separately assess decision versus learning processes. Session 3 evaluated stimulus–response automaticity using a location Stroop task. DS activity correlated with response-selection and not feedback events in Phase 1 (i.e., Blocks 1–3), Session 1. Longer response times (RTs), lower accuracy, and greater inter-trial variability characterized Phase 1, suggesting deliberation. DS activity extinguished in Phase 2 (i.e., Blocks 4–12), Session 1, once RTs, response variability, and accuracy stabilized, though stimulus–response automatization continued. This was signaled by persisting improvements in RT and accuracy into Session 2. Distraction between Sessions 1 and 2 briefly reintroduced response uncertainty, and correspondingly, significant DS activity reappeared in Block 1 of Session 2 only. Once stimulus–response associations were again re-familiarized and deliberation unnecessary, DS activation disappeared for Blocks 2–8, Session 2. Interference from previously learned right or left button responses with incongruent location judgments in a location Stroop task provided evidence that automaticity of stimulus–specific button-press responses had developed by the end of Session 2. These results suggest that DS mediates decision making and not late-stage learning, reconciling two, independently evolving and well-supported literatures that implicate DS in different cognitive functions.

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4.1 Introduction

The dorsal striatum (DS)—the bulk of the caudate nucleus and putamen—has long been implicated in stimulus-response learning (Ashby, Ennis, & Spiering, 2007; Yin & Knowlton, 2006). The DS is ascribed a role in both early, goal-directed learning (Brovelli, Nazarian, Meunier, & Boussaoud, 2011; O'Doherty et al., 2004) as well as late-stage learning of stimulus-response associations to the point of automaticity (Ashby, Turner, & Horvitz, 2010; Balleine, Liljeholm, & Ostlund, 2009). Challenging this notion, however, learning is often preserved in patients (Exner, Koschack, & Irle, 2002; Nole M. Hiebert, Seergobin, Vo, Ganjavi, & MacDonald, 2014; A. A. MacDonald, Seergobin, et al., 2013; Vo et al., 2014) and in animals (Atallah, Lopez-Paniagua, Rudy, & O'Reilly, 2007) with DS dysfunction. Features of standard stimulus-response learning methodology potentially shed light on this controversy as detailed in the paragraphs below.

4.1.1 Disentangling Learning and Decisions Guided by Learning

Decision-making and learning processes are confounded in standard stimulus-response learning methodologies (Jessup & O'Doherty, 2011; McDonald & Hong, 2004). Trials typically proceed as follows: a) a stimulus is presented and participants decide among a set of responses, and b) feedback regarding accuracy is provided, shaping stimulus-response associations. Learning is generally measured by the accuracy in selecting responses. Consequently, failing either to acquire stimulus-response associations or to select accurate responses based on these learned associations could lead to impaired performance in these paradigms. In this way, in standard paradigms, evaluation of learning and decision making is ambiguous. Further, in functional magnetic resonance imaging (fMRI) studies, a) selecting a response and enacting it, and b) learning from feedback regarding the appropriateness of the response are typically treated as a single event with all significantly activated brain regions ascribed a role in learning *per se* (Dobryakova & Tricomi, 2013; Jessup & O'Doherty, 2011; R. A. Poldrack, Prabhakaran, Seger, & Gabrieli, 1999).

Accordingly, some brain regions that might underlie decision processes guided by learned associations could erroneously be assigned a role in learning. Given that these processes are temporally intertwined and functionally interdependent, distinguishing them is very challenging, requiring novel experimental designs, and nuanced interpretations. Learning and decision selection are entirely distinct processes phenomenologically, however. Distinguishing neural substrates of these different operations is important, with implications for understanding cognition in health and disease.

Recently, we investigated this issue in early, goal-directed learning using fMRI (Nole M. Hiebert, Vo, et al., 2014). Participants learned to associate abstract images with button presses through deterministic feedback. We modeled a) the phase during which participants decided amongst options and selected responses separately from b) the stage when participants learned about associations through feedback regarding the accuracy of their choices. We found activation of DS—specifically the head of the caudate nucleus—only during the decision enactment phase, not during the feedback phase when participants learned the associations based on outcome information. Furthermore, DS activation during the decision stage of our trials only occurred for trials arising later in the learning session, when the slope of learning was shallower but when participants were beginning to have a basis on which to make response selections, guided by associations that they had acquired in the earliest trials. In contrast, activity in the ventral striatum (VS)—consisting of the nucleus accumbens and most ventral parts of the caudate nucleus and putamen—correlated with the feedback phase of our stimulus-response learning trials as has been shown by others (R. Cools, Lewis, Clark, Barker, & Robbins, 2007; Schultz, Apicella, Scarnati, & Ljungberg, 1992). Feedback-related VS activation was greatest in the earliest phase of learning when the slope of behavioural change, indicative of stimulus-response association learning, was steepest.

4.1.2 DS mediates Late-Stage Learning and Automaticity?

The findings of Hiebert et al., (2014b) were a) consistent with the view that DS mediates decisions regarding response selection, and b) inconsistent with the contention that DS mediates early, feedback-based learning, as has previously been prevalently claimed

(Balleine et al., 2009; Boettiger & D'Esposito, 2005; Brovelli et al., 2011; Brown & Stern, 2013; Foerde, Race, Verfaellie, & Shohamy, 2013; Garrison, Erdeniz, & Done, 2013; Hart, Leung, & Balleine, 2013; O'Doherty et al., 2004). However, a role for DS in other forms of learning that do not depend upon feedback or that occur during later stages of stimulus-response association formation could not be ruled out. Indeed, in addition to claims that the DS mediates early learning, the DS, particularly the body and tail of the caudate nucleus, has also been implicated in later stages of learning, when stimulus-response associations are strengthened through repeated experience to the point that they become automatic (Ashby et al., 2007; Helie, Roeder, & Ashby, 2010).

A prominent theory of automaticity suggests that the role of the DS—*specifically the body and tail of the caudate nucleus*—is to acquire associations and train cortical-cortical connections between higher-order sensory and pre-motor areas (Ashby et al., 2007; Helie et al., 2010). This model of automaticity is referred to as Subcortical Pathways Enable Expertise Development (i.e., SPEED; Ashby et al., 2007). SPEED predicts that subcortical regions mediate learning. The theory maintains that the head of the caudate nucleus mediates early learning, and as the associations become more practiced, progressing toward automaticity, more posterior regions of the striatum, namely the body and tail of the caudate nucleus, underlie late-stage learning. Once automaticity has been achieved, involvement of DS ceases, and stimulus-specific, automatic behaviours become mediated by cortical regions (i.e., pre-motor, motor, and visual cortices; Ashby et al., 2007).

Balleine and O'Doherty (2010), however, go further contending that in addition to being implicated in training stimulus-response habits, DS mediates and sustains habitual or automatic responding even once these associations are well-entrenched (Balleine & O'Doherty, 2010; Everitt & Robbins, 2005; Tricomi, Balleine, & O'Doherty, 2009). Though several human studies of habit learning ascribe habit formation to DS (i.e., dorsal putamen), closer examination reveals that the ventral, posterior putamen (e.g., peak coordinates $z = 0$) is often the region preferentially activated during these pivotal learning studies (Balleine & O'Doherty, 2010; Tricomi et al., 2009; but see Wunderlich, Dayan, & Dolan, 2012, implicating dorsal putamen). It is widely accepted that VS and DS are functionally distinct (Atallah et al., 2007; P. A. MacDonald & Monchi, 2011; van der Meer

& Redish, 2011). Indeed, others explicitly claim that posterior ventral putamen (i.e., VS) mediates overlearning of motor responses (Jueptner, Frith, Brooks, Frackowiak, & Passingham, 1997; Lehericy et al., 2005).

In a study implicating DS in the development of automatic behaviours, Helie et al. (2010) investigated automatization of responses in a category learning paradigm that included over 10,000 trials, across 20 separate learning sessions, with fMRI data obtained in Sessions 1, 4, 10, and 20. They found that activity in DS was increased throughout Session 1, at the end of which high levels of response accuracy were ultimately achieved (i.e., 89.6%). In subsequent sessions, DS activity was significantly attenuated (i.e., after Session 1) whereas cortical activation continued to correlate with accurate categorization even after extensive training. Only neural activity correlating with stimulus-response events (i.e., the time period from the onset of the stimulus to the button-press response) were examined. Given the confounding of decision and learning processes in these methodologies and consistent with our claim in Nole M. Hiebert, Vo, et al. (2014), DS activation at the time of response selection and enactment could have arisen due to its involvement in decision-making processes and not with association learning *per se*. Several other studies cited as support for the SPEED model can be re-interpreted similarly to the findings of Helie et al. (2010), concluding that DS activation arises not due to its role in learning but rather due to its role in decision-making processes (R. A. Poldrack et al., 2005; Wu, Kansaku, & Hallett, 2004). As with studies of early stimulus-response learning, most experiments investigating DS's role in late-stage learning combine and confound learning processes and stimulus-specific response-selection processes (O'Doherty et al., 2004; Tricomi et al., 2009).

4.1.3 DS mediates Decision Making?

Indeed, a re-interpretation of these early- and late-learning experiments, considering the facts that decision making and stimulus-response association learning a) depend upon one another to produce accurate performance, and b) are often merged in fMRI studies, could integrate two divergent and extensive literatures regarding DS's role in cognition. Increasingly, DS is linked to response selection and decision making (Atallah et al., 2007; Grahn, Parkinson, & Owen, 2009; Jessup & O'Doherty, 2011; A. A. MacDonald et al.,

2014). Decision making is defined as the process of representing and assigning values to different response possibilities, then selecting and executing the most appropriate action (Rangel, Camerer, & Montague, 2008). DS has particularly been ascribed a role in decision making when decisions require a degree of reflection, when there is some ambiguity, and when cognitive control or flexibility are required. This process is referred to as *deliberation* (Ali, Green, Kherif, Devlin, & Price, 2010; R. Cools & D'Esposito, 2011; Daniel et al., 2010; DeGutis & D'Esposito, 2007; P. A. MacDonald et al., 2011; Ohira et al., 2010; Robertson, Hiebert, Seergobin, Owen, & MacDonald, 2015). In this way, DS is implicated prominently in this literature in *resisting* habitual responding or attending to more salient stimuli (Balleine et al., 2009; Benke, Delazer, Bartha, & Auer, 2003; Cameron, Watanabe, Pari, & Munoz, 2010; R. Cools, 2006; Roshan Cools, Rogers, Barker, & Robbins, 2010; Nole M. Hiebert, Vo, et al., 2014; P. A. MacDonald et al., 2011; Rieger, Gauggel, & Burmeister, 2003; Robertson et al., 2015), completely at odds with the independently-evolving literature linking DS with stimulus-response learning and automatization.

In categorization tasks, DS activity, assessed with neuroimaging, correlates with decision accuracy when options need to be weighed but not once responses become so well-practiced that reflection is unnecessary (Helie et al., 2010; Soto, Waldschmidt, Helie, & Ashby, 2013). Preferential DS activation is observed for ambiguous relative to unambiguous decisions (DeGutis & D'Esposito, 2007; P. A. MacDonald et al., 2011; Schouppe, Demanet, Boehler, Ridderinkhof, & Notebaert, 2014), supporting a role for DS in the process of deliberation. Further, patients with DS dysfunction are *less* impaired than healthy control participants at attending to more salient stimuli among distractors and choosing more practiced responses among competing alternatives (Cameron et al., 2010; R. Cools, Rogers, Barker, & Robbins, 2009; Hood et al., 2007), but they are *more* impaired when they are required to select less salient stimuli or perform less automatic responses relative to alternatives (Benke et al., 2003; Cameron et al., 2010; R. Cools, Altamirano, & D'Esposito, 2006; R. Cools et al., 2009; Hood et al., 2007; Rieger et al., 2003; Thoma, Koch, Heyder, Schwarz, & Daum, 2008), suggesting that DS's role in decision making is to promote deliberation and prevent poorly considered or impulsive choices. These claims are at odds with prevalent theories ascribing a role for DS in automatization of responses

and selection of habitual actions (Everitt & Robbins, 2005) and therefore requires direct investigation to reconcile these contradictory contentions regarding DS's role in cognition.

4.1.4 Current Study

Here, we critically tested the claim that DS mediates automatization of stimulus-specific responses versus the notion that it underlies deliberation during action selection. We investigated later-stage, stimulus-response learning, once performance accuracy was greater than 90%. We estimated striatal brain activity using fMRI along with behaviour during later-stage, stimulus-response learning. We further included an explicit measure of whether stimulus-response associations achieved automaticity. We closely paralleled Nole M. Hiebert, Vo, et al. (2014), but used fewer stimuli and only two responses, right or left button presses. Further, we began with an explicit learning phase—a shortcut to late-stage learning—during which all stimuli in the experiment were presented and assigned to either the right or left button press. Subsequently, as in Nole M. Hiebert, Vo, et al. (2014), stimulus-response learning took place in an implicit, feedback-based manner (Session 1), followed by further implicit strengthening of these associations through repeated stimulus-response trials with feedback removed (Session 2). We investigated neural activity for decision-making and feedback events separately in Session 1 and for decision-making events only in Session 2. Between Sessions 1 and 2, we implemented a 20-minute distractor task with the aim of 1) testing whether stimulus-response automaticity was achieved by the end of Session 1, and 2) re-introducing an element of uncertainty and deliberation for decisions in Block 1 of Session 2. The appearance of preferential blood-oxygenation-dependent (BOLD) signal in DS immediately following distraction therefore could critically distinguish between notions that DS mediates the development of stimulus-response association automaticity versus decisions requiring reflection. Finally, Session 3 consisted of a location Stroop task as a second, objective test of whether stimulus-specific responses were automatized following Sessions 1 and 2. In this final session, participants indicated the location, with right or left button presses, of stimuli that had previously been paired with right or left button-press responses during learning Sessions 1 and 2 versus novel stimuli.

We also performed a second, supplemental experiment using a similar protocol to the one summarized in the preceding paragraph, to further clarify our findings (See 2.6). Experiment 2 differed from the Main Experiment in the following ways: 1) neural activity was not estimated with fMRI, 2) an additional session of the modified location Stroop task was also included immediately after Block 3 (i.e., Phase 1, explained below) in Session 1.

4.1.5 Predictions

If DS underlies the development of automaticity as suggested by SPEED, BOLD signal in DS should persist for stimulus-specific responses until associations achieve automatic status (i.e., throughout Session 1, and possibly in Session 2 depending on explicit measures of automaticity). We included two measures of stimulus-response automaticity. At the end of Session 1, we examined the effect of an intervening task on stimulus-response performance and BOLD signal. If automaticity had developed prior to the end of Session 1, response time (RT), accuracy, and BOLD signal should be unchanged from Phase 2, Session 1 and Session 2 despite an intervening distraction (See Ashby et al., 2010, for a review). At the end of Session 2, we investigated facilitation and interference in a location Stroop task, related to automaticity of previously-learned, stimulus-specific right and left button presses. If automaticity had developed by the conclusion of Sessions 1 and/or 2, a) faster RTs and/or reduced errors should occur when location button presses matched the button press that had previously been associated with the stimulus in Sessions 1 and 2, and/or b) slower RTs and/or increased errors should occur when location button presses mismatched the button press that had previously been associated with the stimulus in Sessions 1 and 2.

In contrast, if DS mediates deliberation in response selection, DS activity should be maximal in very early phases of the Main Experiment when decision making requires greater consideration, indexed by longer RTs, lower accuracy, and greater response variability (Phase 1, Session 1). Response variability was measured by changes in standard deviation of RTs (SD). Activity in DS should attenuate and disappear, even prior to achievement of automatic responding, once responses become sufficiently well-learned that deliberation is unnecessary (Phase 2, and Session 2), signaled by reduced RT,

accuracy, and/or response variability. To further distinguish these views, following an unrelated, intervening task, DS BOLD signal is expected to a) re-appear in the first block when response deliberation would again be required (i.e., Block 1, Session 2) but b) quickly attenuate due to savings when responses again became well-practiced (Blocks 2-8, Session 2).

Disputing the claim that DS underlies late-stage learning to the point of stimulus-response automaticity using fMRI can only be accomplished by showing that DS BOLD signal is dissociated from this process, attenuating *before* automaticity of stimulus-response associations is actually achieved. In this way, this well-entrenched view about DS's role in behaviour can only be contested by accepting a null result. There is a, perhaps, justified bias against publishing negative findings, in that with frequentist approaches, the probabilities of Type II (i.e., falsely failing to reject the null hypothesis) and Type I errors (i.e., falsely rejecting the null hypothesis) are asymmetric. Type I errors are set a clear maximum, usually less than 0.05, whereas the former varies across studies in terms of its magnitude and determinants (Dienes, 2014) not pre-determined by the experimenter. However, this systematic publication bias contributes to extremely slow changes to the status quo with the effect that once a claim is disseminated and relatively accepted, it becomes nearly irrefutable, a process referred to as *canonization* (Nissen, Magidson, Gross, & Bergstrom, 2016). Findings at odds with prevailing views are considered less publication-worthy and held to a far higher standard (Nissen et al., 2016). Computational models, however, reveal that selective publication and omission of negative results does not improve efficiency or accuracy of scientific inquiry, but does increase false canonization (Nissen et al., 2016; van Assen, van Aert, Nuijten, & Wicherts, 2014). These concerns notwithstanding, to critically test the contention that DS underlies late learning versus deliberation in action selection and to increase confidence in our results, we have introduced a number of manipulations (e.g., distraction separating Sessions 1 and 2) that should predictably alter behaviour and DS BOLD signal in distinct ways to dissociate the differing accounts of DS's role in cognition. Further, in addition to frequentist statistical approaches, we planned to investigate our effects using a Bayesian analysis that allows directly contrasting the probability of the null and the alternative hypotheses in a

symmetrical way, putting these hypotheses on an equal footing, and directly comparing the relative fit of the two models (Dienes, 2014). This approach would allow us greater confidence in our interpretation of null results if they arose, as we predicted.

4.2 Materials and Methods

4.2.1 Participants

Nineteen healthy, young, right-handed adults participated in this experiment (10 males, 9 females). Participants abusing prescription or illicit drugs, alcohol, or taking cognitive-enhancing medications including methylphenidate were excluded from participating in the experiment. The Health Sciences Research Ethics Board of the University of Western Ontario approved this study. All participants provided informed, written consent to the approved protocol before beginning the experiment, according to the Declaration of Helsinki (2013).

4.2.2 Procedures

At the outset, all participants explicitly learned to associate six abstract images with one of two button-press responses prior to fMRI Sessions 1, 2, and 3. Images consisted of characters taken from the invented *Klingon* alphabet (Figure 4.1). The six abstract images appeared on the screen. Three were labelled “left button press” and the other three were labelled “right button press”. Participants were given three minutes to memorize the label given to the images as best they could.

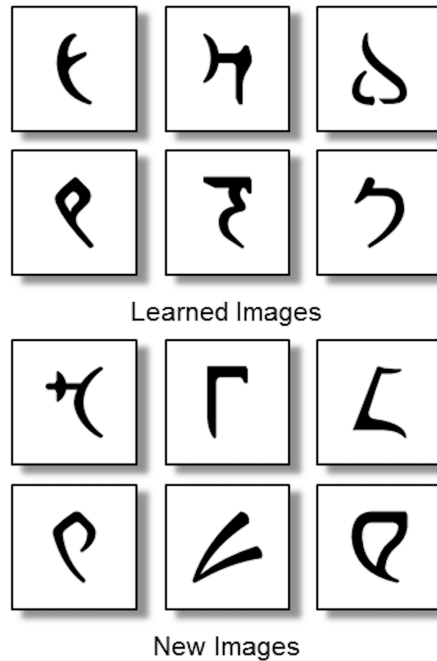


Figure 4.1 Abstract images presented in the experiment.

Learned images refer to the images that were studied and associated with a specific 'right' or 'left' button-press response at baseline, via deterministic feedback in Session 1, and in Session 2. In Session 3 (3A and B in Experiment 2), these learned images created the conditions for the congruent and incongruent conditions depending on their location of presentation. New images refer to the images presented only in Session 3 (i.e., 3A in the Main Experiment and 3A and 3B in Experiment 2) that constituted the control condition.

Figure 4.2 depicts the experimental protocol of the Main Experiment. In Session 1, on every trial, one of the six stimuli presented in the baseline learning session appeared in the centre of the projection screen. Participants were asked to perform the button-press response that had been assigned to the stimulus. For stimuli assigned to a left button press, participants were instructed to press the left button on the button box with their index finger. For stimuli assigned to the right button press, participants were asked to press the right button on the button box with their middle finger. All responses were performed with the right hand. Deterministic feedback regarding the accuracy of the response was then provided (i.e., 'Correct' or 'Incorrect') during a feedback event. Trials were organized into four scanning runs, with each run consisting of three blocks of 18 trials, for a total of twelve blocks and 216 trials. Each abstract image occurring three times in random order per block.

At the end of the twelfth block, participants were given a score summarizing their overall performance.

A Main Experiment

Explicit	Session 1		Distraction	Session 2		Session 3
	Phase 1	Phase 2		Block 1	Blocks 2–8	

B Experiment 2

Explicit	Session 1	Session 3A	Session 1	Distraction	Session 2		Session 3B
	Phase 1		Phase 2		Block 1	Blocks 2–8	

Periods of expected deliberation
 Sessions measuring automaticity

Figure 4.2 Experimental protocol.

A) In the Main Experiment, participants learned to associate six abstract images with either a 'left' or 'right' button press response explicitly in the block named Explicit. In Session 1, participants saw each image and performed the learned response individually in the presence of feedback. Due to longer RTs, lower accuracy, and increased response variability, the first three blocks (referred to as Phase 1) were analyzed separately from Blocks 4-12 (i.e., Phase 2). After completing a distractor task for 20 minutes, participants performed Session 2 where they practiced the learned responses to the images in the absence of feedback. We expected response uncertainty to reappear in Block 1, Session 2 and we therefore analyzed it separately from Blocks 2-8, Session 2. Session 3 served as an objective measure of automaticity and was performed after Session 2 concluded. **B)** Experiment 2 followed the same protocol as the Main Experiment except that the presence of automaticity was measured both after Phase 1, Session 1 and after Session 2 (Session 3A and 3B respectively). Areas in grey represent periods where response deliberation is expected and areas in black denote the modified Stroop task (i.e., objective measure of automaticity).

Trials in Session 1 proceeded as follows: (i) a cross appeared in the centre of the projection screen for 700 ms; (ii) a blank screen occurred for 300 ms; (iii) an abstract image was presented in the centre of the projection screen until a button-press response; (iv) a blank screen appeared for a variable period of time sampled from an exponential distribution (mean: 2500 ms; minimum: 525 ms; maximum: 7000 ms); (v) feedback (i.e., 'Correct' or 'Incorrect') appeared for 1000 ms; (vi) a blank screen appeared for a variable period of time sampled from an exponential distribution (mean: 2500 ms; minimum: 525 ms;

maximum: 7000 ms). The inter-stimulus interval (ISI) and inter-trial interval (ITI) were jittered between the response and feedback, and between the offset of feedback and the beginning of the subsequent trial, respectively, to create two fMRI events within each trial: a) the stimulus-response event and b) the feedback event. The stimulus-response or decision-making event included the presentation of the abstract image until the participant made a button-press response. The feedback, or learning event included the presentation of feedback. Rest events were also created and modelled as regressors and consisted of ITIs only (Figure 4.3A).

Between Sessions 1 and 2, participants performed a 20-minute visual-spatial working memory task as a distraction from the main task. The task consisted of prime and probe pairs in which participants indicated, with a button press, whether an array of dots inside a grid pattern was the same or different across the prime and probe trials. The distractor task was included to re-introduce an element of uncertainty and deliberation in selecting responses in the first block of Session 2.

In Session 2, on every trial, participants performed a right or left button press in response to the image that appeared in the center of the screen. The images were the same six Klingon characters presented at the start of the experiment and in Session 1. Participants were asked to make the button-press responses that they had learned explicitly at the outset of the experiment and through Session 1 in Session 2. No feedback was provided, to preclude further feedback-based learning during Session 2. Participants performed eight blocks of 18 trials each, spaced across two scanning runs, four blocks per run. In total, Session 2 consisted of 144 trials. Trial parameters for Session 2 were otherwise identical to those in Session 1 (Figure 4.3B).

In Session 3, the six images associated with left or right button-press responses explicitly at the outset of the experiment and throughout Sessions 1 and 2 were presented along with six new *Klingon* characters. Images were presented one at a time, in random order. These images were presented either to the left or the right of centre, with a distance away from centre equal to the width of the image. Participants responded to the location of the stimulus with the left (i.e., index finger) or right (i.e., middle finger) button-press response.

No feedback was provided in this session. Participants performed 4 blocks of 36 trials each, spaced across two scanning runs, two blocks per run. In total, Session 3 consisted of 144 trials and no feedback was provided. Trial parameters were similar to Sessions 1 and 2 (Figure 4.3C).

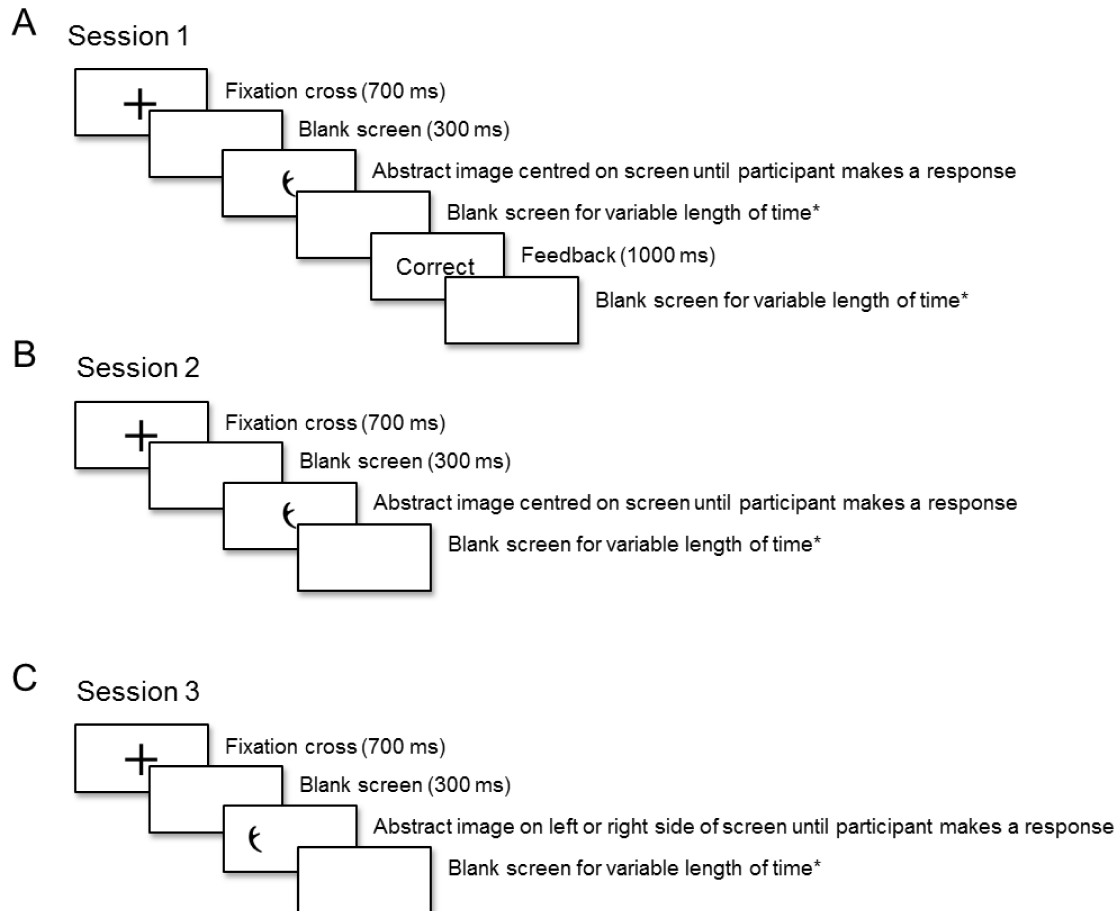


Figure 4.3 Example of a single trial in Sessions 1, 2, and 3 in the experiment.

A) Participants learned to associate six abstract images with either a 'left' or 'right' button-press response in Session 1. The following is an example of a trial: (i) a cross appeared in the centre of the projection screen for 700 ms; (ii) a blank screen occurred for 300 ms; (iii) an abstract image was presented in the centre of the projection screen until a button-press response; (iv) a blank screen appeared for a variable period of time sampled from an exponential distribution (mean: 2500 ms; minimum: 525 ms; maximum: 7000 ms); (v) feedback (i.e., 'Correct' or 'Incorrect') appeared for 1000 ms; (vi) a blank screen appeared for a variable period of time sampled from an exponential distribution (mean: 2500 ms; minimum: 525 ms; maximum: 7000 ms). **B)** Participants recalled the responses to the learned images in the absence of feedback in Session 2. **C)** Images appeared left or right of centre, at a distance equal to the width of the image away from centre, and

participants indicated the location of the images with a left or right button-press response. Stimuli included the six learned images presented at baseline and in Sessions 1 and 2 as well as six new images. Trials in Sessions 2 and 3 were identical to Session 1 except that feedback was omitted in both and the images appeared off centre in Session 3. * The inter-stimulus and inter-trial intervals (ISI and ITI, respectively) were jittered between the response and feedback and between the offset of feedback and the beginning of the subsequent trial to create two fMRI events within each trial: a) the stimulus-response event and b) the feedback event for Session 1. In Sessions 2 and 3, the ITIs were jittered between the response and the subsequent trial.

4.2.3 Behavioural Data Analysis

To examine changes in RT, SD of RTs across blocks, and accuracy across Sessions 1 and 2, single-factor repeated measures analyses of variance (ANOVAs) were run with block (Session 1: 12 blocks; Session 2: 8 blocks) as the within-subject variable. RT was the time between the onset of the abstract image and the button press by the participant measured in milliseconds (ms). The number of correct “right” and “left” button-press responses recorded after each block was our estimate of accuracy.

Three conditions—congruent, incongruent, and control—were created in Session 3. In the congruent condition, an image appeared in a location that was consistent with the left or right button-press response learned for that image at baseline and in Session 1, and practiced in Session 2. In the incongruent condition, a stimulus appeared in a location that was inconsistent with the left or right button-press response learned at baseline and in Session 1, as well as practiced in Session 2. In the control condition, six new images that were not previously presented in the experiment appeared to the left or right of centre. Session 3 consisted of 48 congruent, 48 incongruent, and 48 control trials that occurred in random order. All old and new stimuli appeared left and right of centre equally often. RTs were measured from the onset of the image until the button-press response in ms. The control condition provided a baseline measure of accuracy and latency for providing a location response. Facilitation was calculated as mean RTs or error rates in the congruent condition minus those in the control condition and interference was calculated as mean RTs or error rates in the incongruent condition minus those in the control condition. Lastly, congruent and incongruent trials together were contrasted with control trials to assess trials that involved previously-learned stimuli that could distract from choosing location

responses versus the condition in which there were no previously-learned stimulus-identity responses to distract from location responses.

One sample *t*-tests were run on the facilitation and interference scores to assess if they were significantly different from zero. These analyses provided an objective test of whether the stimulus-response associations had been learned to the point that the responses were automatic.

4.2.4 Imaging Acquisition

fMRI data were collected on a 3 Tesla Siemens Magnetom Prisma with Total Imaging Matrix MRI at Robarts Research Institute at the University of Western Ontario. A scout image for positioning the participant and a T1 for anatomical localization were first obtained. Session 1 consisted of four runs of T2*-weighted functional acquisitions. Each run consisted of three blocks of 18 trials. A distractor task (20 minutes) was administered after Session 1. Session 2 consisted of two experimental runs. Each run comprised four blocks of 18 trials. Session 3 was completed as the final session and consisted of two experimental runs, with each run containing 2 blocks of 36 trials. In each of the experimental sessions, the repetition time was 2.5 s with one whole brain image consisting of 43, 2.5 mm-thick slices. The field of view was oriented along the anterior and posterior commissure with a matrix of 88×88 pixels, with an isotropic voxel size of $2.5 \times 2.5 \times 2.5$ mm³. The echo time was 30 ms and the flip angle was 90°.

4.2.5 fMRI Data Analysis

Matrix Laboratory (MATLAB, MathWorks, Inc., Natick, Massachusetts, United States) was used in conjunction with Statistical Parametric Mapping version 8 (SPM8; Wellcome Department of Imaging Neuroscience, London, United Kingdom) to complete fMRI analysis. Images were slice-time corrected, reoriented for participant motion, spatially normalized to the standard Montreal Neurological Institute (MNI) template, smoothed with an 8 mm full-width half-maximum Gaussian kernel, and high-pass filtered (0.0078 Hz).

Fixed effects analyses were used to model individual participant's data in SPM8. Regressors were created by convolving onsets and durations of stimulus-response, feedback, and rest (i.e., the ITI) events with the canonical hemodynamic response function. The stimulus-response event was defined as the time from onset of the *Klingon* character until the participant made a button-press response. The feedback event was defined as the duration of feedback (i.e., "Correct" or "Incorrect") presentation (i.e., 1000 ms from onset to offset). The rest period modelled was the time between the offset of the feedback until the fixation point of the subsequent trial (i.e., the ITI). A general linear model (GLM) was created for Session 1 events and included regressors for stimulus-response, feedback, and rest events for Session 1 and investigated regional BOLD activity associated with these events. There were twelve regressors for each of the three events, corresponding to each of the twelve blocks in Session 1. Six rigid-body realignment parameters were entered as nuisance regressors to minimize the effect of head motion. A similar model was created for stimulus-response and rest events for Session 2. There were a total of 16 regressors, two per block, eight of which corresponded to stimulus-response events and the other eight for rest events. Motion regressors were also included in the Session 2 GLM.

To investigate learning versus deliberation-related brain activity, contrasts at the group level were created, examining activity early and late in Session 1 for both stimulus-response and feedback events. Given the significant decreases in RT, SD of RTs, and significant increases in accuracy in Session 1 across the first three blocks, that subsequently levelled off (See Figure 4.4A), Blocks 1-3 were assigned early status, referred to as Phase 1, and Blocks 4-12 were considered late, referred to as Phase 2. Similarly, for Session 2, we investigated Block 1 and Blocks 2-8 separately, with the expectation that a 20-minute distractor task might re-introduce an element of consideration in stimulus-response selection but only for the earliest block due to savings and substantial previous experience with the stimulus-response pairs.

For Session 3, regressors were created convolving onsets and durations of congruent, incongruent, and control trials. At the group level, activation correlating with facilitation and interference was investigated by contrasting activation of congruent with control trials for facilitation and incongruent with control trials for interference.

Peaks within the striatum were reported at a significance level of $q < 0.05$ cluster-corrected using false discovery rate (FDR) correction unless otherwise indicated. Striatal regions were defined using the Harvard-Oxford Subcortical Atlas in the FMRIB Software Library version 5.0 (FSL v5.0; Analysis Group, FMRIB, Oxford, United Kingdom). VS and DS are not distinct anatomical structures, which creates difficulty when attempting to separate them in an fMRI context. In a review, Postuma and Dagher (2006) define VS as $z \leq 2$, which we employed. Here, DS refers to portions of the caudate nucleus and putamen at a level of $z > 2$ in MNI space. VS was defined as the nucleus accumbens, and the caudate nucleus and putamen at a level of $z \leq 2$ in MNI space. All cortical regions were defined using the Harvard-Oxford Cortical Atlas in the FMRIB Software Library version 5.0 (FSL v5.0; Analysis Group, FMRIB, Oxford, United Kingdom). All x , y , z coordinates are reported in MNI space.

The contrasts of interest for Sessions 1, 2, and 3 were as follows: (i) stimulus-response events versus rest in Phase 1 of Session 1; (ii) feedback events versus rest in Phase 1 of Session 1; (iii) stimulus-response versus feedback events in Phase 1 of Session 1; (iv) stimulus-response events versus rest in Phase 2 of Session 1; (v) feedback events versus rest in Phase 2 of Session 1; (vi) stimulus response versus feedback events in Phase 2 of Session 1; (vii) stimulus-response events of Phase 1 versus stimulus-response events of Blocks 4, 5, and 6, Blocks 7, 8, and 9, and Blocks 10, 11, and 12 of Session 1; (viii) stimulus-response events in Block 1 of Session 2 versus rest; (x) stimulus-response events for Blocks 2-8 versus rest; (xi) stimulus-response events for Block 1 versus Block 8 of Session 2; (xii) facilitation in Session 3; (xiii) interference in Session 3; and (xiv) congruent and incongruent versus control trials in Session 3. Phase 1 refers to Blocks 1-3 in Session 1 and Phase 2 refers to Blocks 4-12 in Session 1, based on behavioural data patterns presented below.

4.2.6 Bayesian Analysis

Bayesian analyses were performed. Bayes' factor one-sample t -tests were conducted using the average beta values extracted in each block of Sessions 1 and 2, and for all contrasts of conditions (i.e., congruent, incongruent and control) in Session 3, using a bilateral dorsal

caudate nucleus ROI. The dorsal caudate nucleus anatomical ROI was created using the Automated anatomical labeling atlas (Tzourio-Mazoyer et al., 2002), and WFU PickAtlas (Maldjian, Laurienti, Kraft, & Burdette, 2003) in conjunction with MarsBaR (Brett, Anton, Valabregue, & Poline, 2002). The ROI included left and right dorsal caudate nucleus at a level of $z > 2$ mm in MNI space. With a test value of zero, the Bayesian analysis examined whether the extracted beta values were significantly greater than zero using the Bayes' factor of three, previously indicated to be the Bayesian corollary of $p < 0.05$ in frequentist hypothesis testing (Dienes, 2014). If the Bayes' factor of the average beta values is less than three, it strongly supports the null hypothesis, that the activation level is not greater than zero.

4.3 Results

4.3.1 Demographic Data

Participants had a mean (standard error measure; SEM) age and duration of education of 23.56 (0.83) and 16.63 (0.46) years, respectively. One participant was excluded from analysis due to excessive head motion while in the scanner, whereas another was excluded for falling asleep in the scanner. Two participants were subsequently excluded from Session 3 only, due to a misinterpretation of the task instructions. 18 participants were included in the analysis of Session 1 and 2, and 16 participants were included in the Session 3 analysis.

4.3.2 Behavioural Data

RT was measured as the time between the onset of the abstract image and a button-press response by the participant in ms. The number of correct “left” and “right” button-press responses recorded after each block provided our measure of accuracy. Behavioural results are presented in Figures 4.4 and 4.5, and Tables 4.1 and 4.2.

4.3.2.1 Session 1

The mean block RT, SD of RTs across blocks, and accuracy across Session 1 are shown in Figure 4.4A-C respectively. Mauchly's test was significant, indicating the assumption of sphericity was violated ($p < 0.001$). Therefore, degrees of freedom were corrected using the Greenhouse-Geisser Epsilon for the RT, SD of RTs across blocks, and accuracy single-factor repeated measures ANOVAs.

Table 4.1 Significant pairwise comparisons for RT, SD, and accuracy differences by block in Session 1.

Block A	Block B	RT		SD		Accuracy	
		<i>t</i> stat	<i>p</i> value	<i>t</i> stat	<i>p</i> value	<i>t</i> stat	<i>p</i> value
1	3	3.73	0.002	3.43	0.005	3.06	0.008
	4	4.07	<0.001	4.32	0.001	-	-
	5	4.07	<0.001	4.09	0.002	3.39	0.004
	6	4.07	<0.001	4.39	0.001	3.39	0.004
	7	4.07	<0.001	3.45	0.005	3.39	0.004
	8	4.07	0.001	3.90	0.002	3.39	0.004
	9	4.07	<0.001	4.26	0.001	2.75	0.015
	10	4.07	<0.001	5.28	<0.001	3.20	0.006
	11	3.39	0.004	4.76	<0.001	>4.07	<0.001
	12	-	-	4.35	0.001	2.95	0.010
2	3	2.75	0.015	2.70	0.020	-	-
	4	3.54	0.003	3.59	0.004	-	-
	5	>4.07	<0.001	3.36	0.006	-	-
	6	4.07	0.001	3.67	0.003	-	-
	7	4.07	0.001	2.73	0.020	-	-
	8	3.12	0.007	3.17	0.009	-	-
	9	>4.07	<0.001	3.53	0.004	-	-
	10	4.07	0.001	4.56	<0.001	-	-
	11	2.71	0.016	4.03	0.002	-	-
	12	4.07	0.001	3.62	0.004	-	-
3	5	2.82	0.013	-	-	-	-
	7	>4.07	<0.001	-	-	-	-
	9	3.06	0.008	-	-	-	-
	10	3.06	0.008	-	-	-	-
4	5	>4.07	<0.001	-	-	-	-
	9	2.28	0.038	-	-	-	-
5	6	2.75	0.015	-	-	-	-
	12	3.54	0.003	-	-	-	-
6	9	3.54	0.003	-	-	-	-
7	9	2.25	0.040	-	-	-	-
8	9	3.73	0.002	-	-	-	-
9	10	2.66	0.018	-	-	-	-
	12	3.73	0.002	-	-	-	-
10	12	3.54	0.003	-	-	-	-
11	12	3.00	0.009	-	-	-	-

Only significant ($p < 0.05$) comparisons are reported. The left column labelled Block A lists the blocks that differed significantly from blocks listed in column Block B. RT – response time, SD – standard deviation.

RTs were examined and revealed a main effect of block, $F_{(3, 95)} = 9.34$, $MSE = 63567.54$, $p < 0.001$. Deconstructing this effect using pairwise comparisons revealed significant RT differences between Blocks 1 – 11 versus other subsequent blocks (see Table 4.1 and Figure 4.4A for specific significant comparisons). No differences arose between Block 12 and other blocks. Mean RTs decreased from 867 ms in Block 1 to 749 ms in Block 12.

SD of RTs across blocks, within patients, were investigated, and revealed a main effect of block $F_{(3, 62)} = 5.07$, $MSE = 11919$, $p < 0.001$. Significant SD differences between blocks were examined using pairwise comparisons and revealed significant differences between Blocks 1 – 3 versus other subsequent blocks (See Table 4.1 and Figure 4.4B for specific significant comparisons). No significant differences arose between Blocks 4-12 and other subsequent blocks. Mean SD decreased from 298 ms in Block 1 to 143 ms in Block 12.

The single factor repeated measures ANOVA for accuracy revealed a significant main effect of Block, $F_{(4, 68)} = 3.03$, $MSE = 33.07$, $p = 0.025$. This was explored further using pairwise comparisons (results presented in Table 4.1 and Figure 4.4C). Significant differences existed between Blocks 1 and 2 versus other subsequent blocks in Session 1. No significant differences arose between blocks later than 2 with one another. The average Block 1 score was 95.01%, which increased to 98.54% in Block 12.

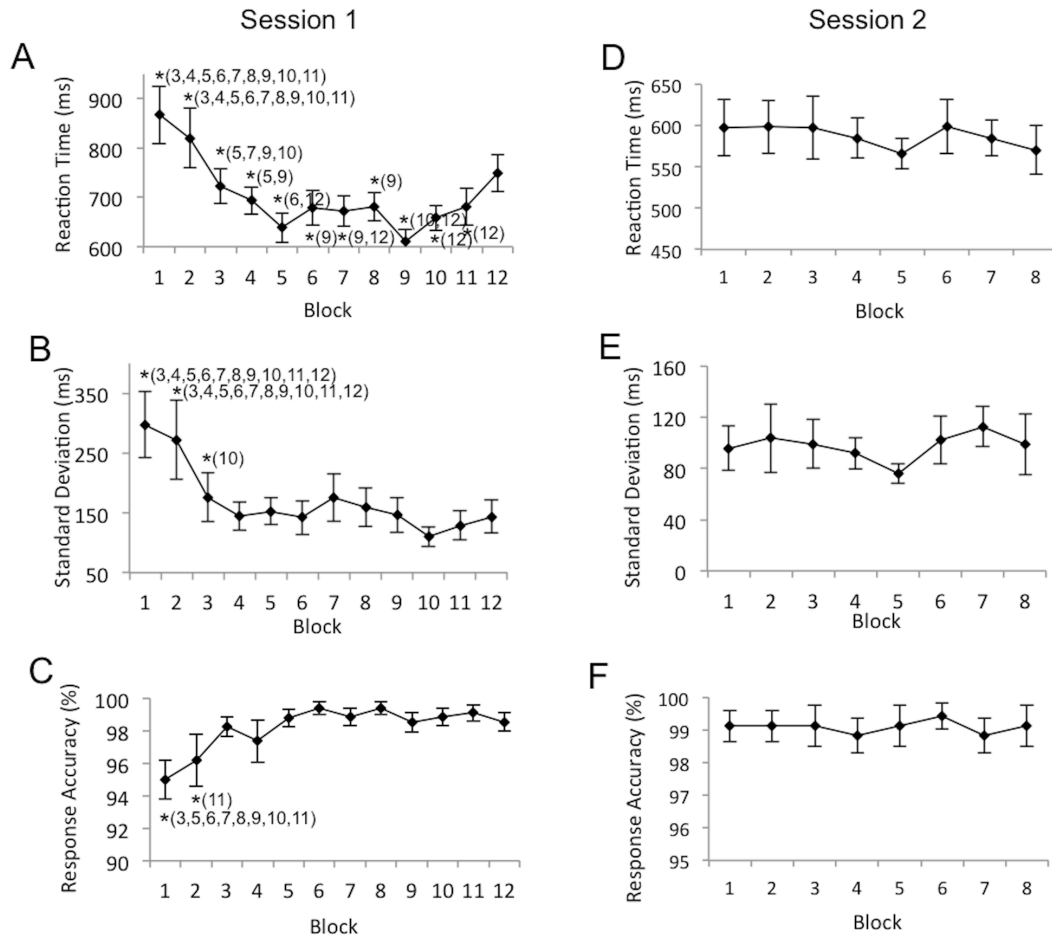


Figure 4.4 Mean response times, standard deviations, and accuracy across Sessions 1 and 2.

A) Mean response times (ms) in each block in Session 1. **B)** Mean standard deviations (ms) calculated using response times in each block in Session 1. **C)** Mean response accuracy (%) in each block in Session 1. **D)** Mean response time (ms) in each block in Session 2. **E)** Mean standard deviations (ms) calculated using response times in each block in Session 2. **F)** Mean response accuracy (%) in each block in Session 2. Error bars represent standard error of the mean. Response time was measured from the onset of the abstract image to the button-press response made by the participant. Response accuracy is a percentage measure of the number of correct button-press responses in a block relative to total number of trials in the block. Significant differences ($p < 0.05$) are indicated with an asterisk (*) and numbers listed next to the asterisk indicate the blocks from which each block differs significantly.

4.3.2.2 Session 2

Mean RT in Block 1, Session 2 was significantly faster than the last block of Session 1 ($t = 1.86, p = 0.044$). Accuracy in Block 1, Session 2 was not significantly different from accuracy in the last block of Session 1 ($t = 0.18, p = 0.429$). Mean block RT, SD of RTs across blocks, and accuracy across Session 2 are presented in Figures 4.4D– F, respectively. As in Session 1, single factor repeated measures ANOVAs were run to investigate differences across Session 2. There were no significant differences across blocks for RT ($F < 1$), SD ($F < 1$), or response accuracy ($F < 1$) across Session 2.

4.3.2.3 Session 3

Data from two participants were excluded from analysis in Session 3 due to reported misinterpretation of the instructions of the task. The error rate in the remaining 17 participants was low (average incorrect responses: 0.74%). Table 4.2 presents the mean RTs and error rates in each of the congruent, incongruent, and control conditions.

Table 4.2 Mean response times and error rates for the congruent, incongruent, and control conditions in Session 3.

Condition	Response Time (ms)	Error Rate (%)
Congruent	378.66 (17.44)	0.73 (0.17)
Incongruent	387.45 (20.66)	1.34 (0.39)
Control	377.84 (18.17)	0.98 (0.50)

Mean (SEM) response times (ms) and error rates (%) are presented. In the congruent condition, an image appeared in a location that was consistent with the left or right button-press response learned at baseline, in Session 1, and practiced in Session 2. In the incongruent condition, a stimulus appeared in a location that was inconsistent with the left or right button-press response learned at baseline, in Session 1, and practiced in Session 2. In the control condition, six new images that were not previously presented in the experiment appeared to the left or right of centre.

Paired t -tests were performed on error rates between congruent and control, and incongruent and control. One sample t -tests were performed on average RT facilitation (i.e., congruent – control), and interference (i.e., incongruent – control; Figure 4.6). There were significantly more errors in incongruent compared to control ($t = 2.06, p = 0.029$) conditions. In addition, RT interference compared to zero trended towards significance (t

= 1.37, $p = 0.095$). However, facilitation ($t = -1.23$, $p = 0.881$) scores did not differ significantly from zero (Figure 4.5).

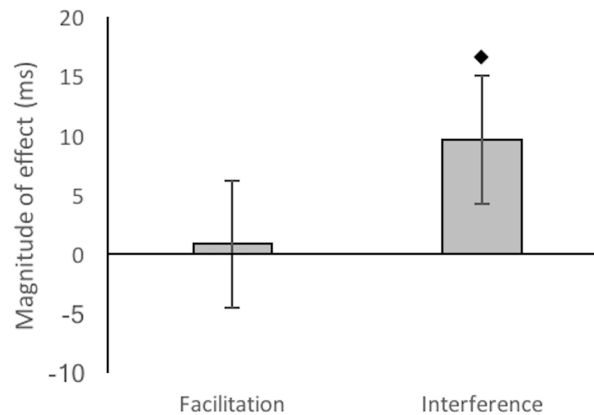


Figure 4.5 Mean facilitation and interference scores in Session 3.

Mean (SEM) facilitation, interference, and incongruent minus congruent difference scores are presented. Facilitation was calculated as mean RTs in the congruent minus control condition and interference was calculated as mean RTs in the incongruent minus control condition. The incongruent minus congruent contrast was also completed. Again, in the congruent condition stimuli were presented in the location that was consistent with the learned left or right button-press responses in earlier sessions. On incongruent trials, stimuli were presented in the location that was inconsistent with the learned left or right button-press responses in earlier sessions. The control condition consisted of new images that the participant had not previously associated with a right or left button-press response. * $p < 0.05$, † $p < 0.1$

4.3.3 FMRI Data

Significant activations are reported at a significance level of $q < 0.05$ FDR corrected unless otherwise stated using SPM5 (Table 4.3-5). In all sessions, error rates were low and therefore only correct responses were examined at the group level. Session 1 contrasts are reported in Table 4.3, Session 2 contrasts are stated in Table 4.4, and Session 3 contrasts appear in Table 2.5. All coordinates (x, y, z) are reported in MNI space. Only significant striatal activations are reported in the text below. Regions of significant activation outside of the striatum are presented in Tables 4.3-5. FMRI contrasts of interest are displayed in Figures 4.6 and 4.7.

4.3.3.1 Session 1

Session 1 was divided into two phases of learning based on behavioural performance. Phase 1 included Blocks 1-3, whereas Phase 2 was comprised of Blocks 4-12. During Phase 1, RTs were longer and accuracy was slightly lower, with greater across-trial variability in these measures than in Phase 2, reflecting response deliberation. During Phase 2, RTs and accuracy had stabilized, indicating that the stimulus-response associations were well-learned and required less consideration at this stage. Session 1 contrasts of interest are reported in Table 4.3.

Table 4.3 Significant brain activations in Session 1 contrasts of interest reported in MNI space.

Contrast	Anatomical Area	Cluster Size	<i>t</i>	<i>q</i>	<i>x, y, z</i>
Session 1: Phase 1					
SR minus rest	Left dorsal caudate nucleus	1108	6.37	<0.001	-18, -1, 25
	Right dorsal caudate nucleus	*	5.54	<0.001	21, -4, 25
	Right occipital fusiform gyrus	5836	7.67	<0.001	48, -64, -20
	Left occipital pole	239	5.76	0.006	0, -97, 16
	Left postcentral gyrus	139	3.93	0.028	-45, -37, 61
FB minus rest	No suprathreshold activations				
SR minus FB	Left dorsal caudate nucleus	152	5.29	0.003	-15, 11, 25
	Right dorsal caudate nucleus	*	3.59	0.028	18, -19, 25
	Right occipital pole	207	6.34	0.001	3, -91, 22
	Right inferior frontal gyrus	72	4.35	0.026	54, 17, -2
	Left juxtapositional lobule cortex	23	5.33	0.020	-6, -1, 58
FB minus SR	Left middle frontal gyrus	23	5.29	0.020	-30, -4, 52
Session 1: Phase 2					
SR minus rest	Left ventral putamen	67	3.58	<0.001	-24, 2, -10
	Right lateral occipital complex	79	4.59	0.022	51, -64, -14
	Right cerebellum	208	4.37	0.001	33, -52, -29
	Left cerebellum	214	4.26	0.001	-39, -61, -23
	No suprathreshold activations				
FB minus rest	Right ventral putamen	*	4.54	0.017	24, 8, -11
SR minus FB	Left supramarginal gyrus	1388	5.28	<0.001	-60, -31, 46
	Left lateral occipital cortex	346	5.10	<0.001	-48, -70, -14
	Right insular cortex	560	4.96	<0.001	39, -1, -2
	Right cuneal cortex	732	4.68	<0.001	0, -79, 25
	Right supramarginal gyrus	251	4.56	<0.001	60, -31, 40
	Right middle frontal gyrus	137	4.55	0.004	36, 35, 43
	Left frontal pole	115	4.48	0.007	-42, 44, 28
	Right middle temporal gyrus	332	4.27	<0.001	51, -52, -2
	No suprathreshold activations				
FB minus SR	No suprathreshold activations				

Session 1: Phase 1 versus Phase 2 for SR events					
Phase 1 minus Blocks 4-6	No suprathreshold activations				
Blocks 4-6 minus Phase 1	Left cingulate gyrus	165	5.08	0.013	-15, -28, 40
	Right parietal operculum cortex	1519	4.43	<0.001	57, -31, 31
	Left insular cortex	855	4.40	<0.001	-30, 29, 7
	Left parietal operculum cortex	355	4.25	0.001	-51, -40, 22
	Right cingulate gyrus	502	4.24	<0.001	9, 14, 34
	Right precuneous cortex	191	4.10	0.008	9, -43, 49
	Left intracalcarine cortex	890	4.01	<0.001	-9, -64, 13
	Right middle frontal gyrus	113	3.88	0.035	27, 35, 28
Phase 1 minus Blocks 7-9	Right dorsal caudate nucleus	267	3.69	<0.001	21, 19, 26
	Left dorsal caudate nucleus	*	3.65	<0.001	-18, 2, 26
	Left precuneous cortex	7451	5.10	<0.001	-9, -64, 16
	Right frontal medial cortex	196	4.57	0.016	6, 35, -14
Blocks 7-9 minus Phase 1	No suprathreshold activations				
Phase 1 minus Blocks 10-12	Right dorsal caudate nucleus	113	4.25	0.013	18, 26, 13
	Left dorsal caudate nucleus	*	4.18	0.004	-12, -1, 25
	Right lateral occipital cortex	969	5.58	<0.001	45, -70, -20
Blocks 10-12 minus Phase 1	Left precentral gyrus	2454	5.99	<0.001	-30, -7, 52
	Left lateral occipital cortex	1539	4.72	<0.001	-51, -73, 19
	Left thalamus	218	4.62	0.005	-3, -19, 1
	Right frontal medial cortex	151	4.21	0.016	3, 38, -14
	Left planum temporale	142	3.86	0.019	-33, -31, 16

Cluster size is reported in voxels. Q values are reported at a significance level of $q < 0.05$ corrected for false discovery rate (FDR) at the cluster-level. T values are reported at the voxel level. Coordinates are reported in MNI space. Striatal regions are presented first and highlighted in each contrast. SR – stimulus-response events; FB – feedback events. *Cluster size unobtainable as peak coordinates are within a larger cluster, q value reported is FDR corrected at the voxel level.

Stimulus-response decisions: Phase 1, Session 1. In Phase 1, significant activation occurred in the left (*peak coordinates*: -18, -1, 25; $t = 6.37$; $q < 0.001$), and right (*peak coordinates*: 21, -4, 25; $t = 5.54$; $q < 0.001$) dorsal caudate nucleus contrasting stimulus-response events with rest periods (Figure 4.6A). Significant activation also occurred in the left (*peak coordinates*: -15, -1, 25; $t = 5.29$; $q = 0.003$) and right (*peak coordinates*: 18, -19, 25; $t = 3.59$; $q = 0.028$) dorsal caudate nucleus contrasting stimulus-response minus feedback events.

Receiving feedback: Phase 1, Session 1. No significant striatal activations arose for feedback events minus rest or stimulus-response events.

Stimulus-response decisions: Phase 2, Session 1. Significant activation occurred in the left ventral putamen (*peak coordinates*: -24, 2, -10; $t = 3.58$; $q < 0.001$) for Phase 2 stimulus-response events minus rest (Figure 4.6B). In addition, significant activation occurred in the right ventral putamen for stimulus-response events minus feedback events (*peak coordinates*: 24, 8, -11; $t = 4.54$; $q = 0.017$). To further explore Phase 2, stimulus-response events were compared to rest at a more liberal criterion of $p < 0.005$ uncorrected for multiple comparisons with a cluster threshold of 10 contiguous voxels. Even using this liberal criterion, no peaks in the DS were revealed. Some activation related to the peak in the left ventral putamen extended dorsally into DS but only at this lessened criterion (*peak coordinates*: -27, 5, -7; $t = 3.70$; $p < 0.001$).

Receiving feedback: Phase 2, Session 1. No significant activation occurred during Phase 2 for feedback events minus rest, or feedback minus stimulus-response events.

Stimulus-response decisions: Phase 1 versus Phase 2. Given that Phase 1 consisted of the first three blocks and Phase 2 was composed of the last nine blocks (Block 4-12), contrasts were made between Phase 1 and Phase 2, grouped into three consecutive blocks, to create balanced contrasts. No significant striatal activations occurred in the Phase 1 minus Blocks 4, 5, and 6 contrast, or the reverse contrast. Significant activation arose in the left and right dorsal caudate nucleus (*peak coordinates*: -18, 2, 26; $t = 3.65$; $q < 0.001$, and *peak coordinates*: 21, -19, 26; $t = 3.69$; $q < 0.001$, respectively), for Phase 1 minus Blocks 7, 8, 9, and for Phase 1 minus Blocks 10, 11, and 12 (*peak coordinates*: -12, -1, 25; $t = 4.18$; $q = 0.004$, and *peak coordinates*: 18, 26, 13; $t = 4.25$; $q = 0.013$, respectively; Figure 4.6C) contrasts. No significant striatal activation occurred during the reverse contrasts (Figure 4.6D).

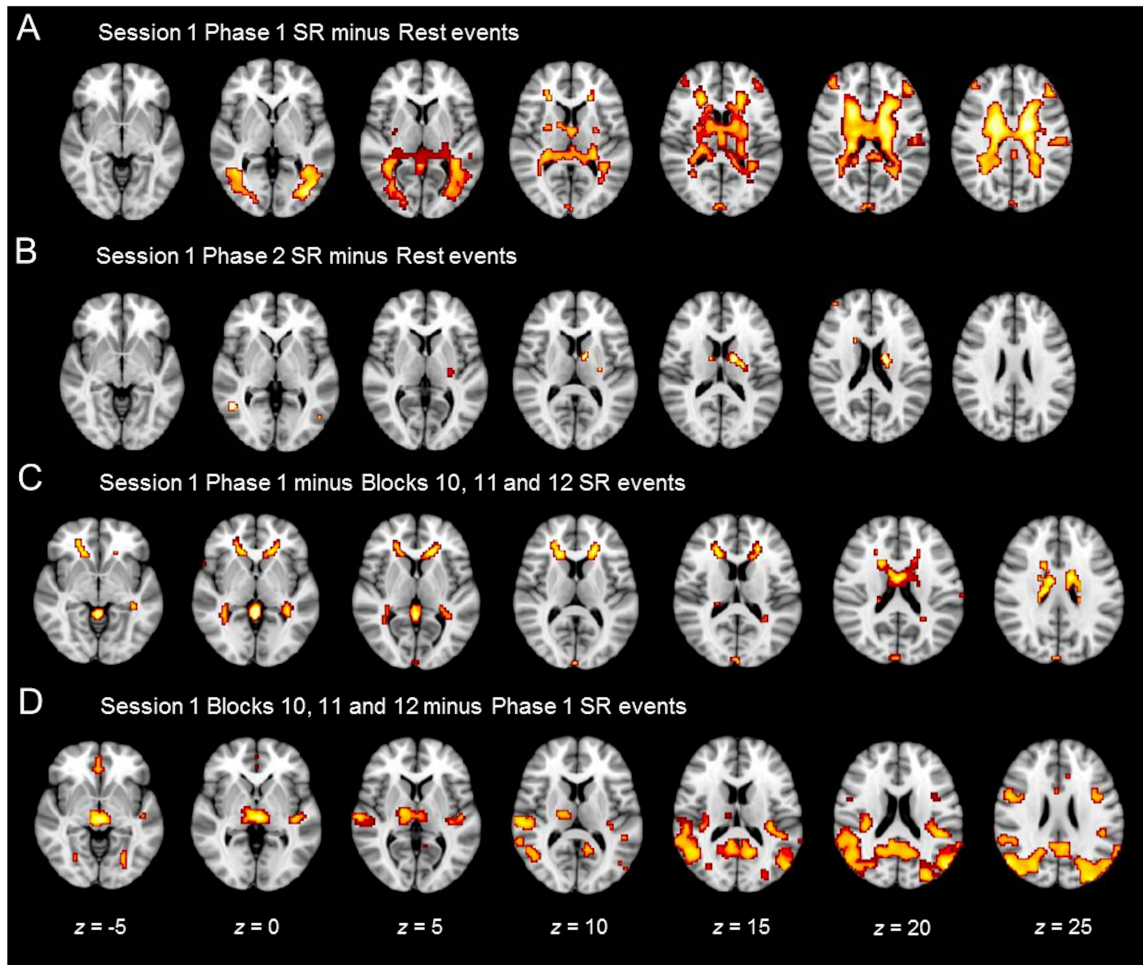


Figure 4.6 Significant activations in contrasts of interest in Session 1 Phases 1 (i.e., Blocks 1-3) and 2 (i.e., Blocks 4-12): SR events.

The figure shows significant activation at a threshold of $q < 0.05$ corrected for false discovery rate (FDR). In each contrast of interest, horizontal slices are presented ranging from $z = -5$ to $z = 25$, every 5 mm. **A)** BOLD signal for stimulus-response minus rest events in Phase 1 of Session 1. **B)** BOLD signal for stimulus-response minus rest events in Phase 2 of Session 1. **C)** BOLD signal for Phase 1 minus Blocks 10, 11, and 12 of Session 1 stimulus-response events. **D)** BOLD signal for Blocks 10, 11, and 12 of Session 1 minus Phase 1 stimulus-response events. SR – stimulus-response events.

4.3.3.2 Session 2

Session 2 contrasts of interest are reported in Table 4.4.

Table 4.4 Significant brain activations in Session 2 contrasts of interest reported in MNI space.

Contrast	Anatomical Area	Cluster Size	<i>t</i>	<i>q</i>	<i>x, y, z</i>
Block 1 minus rest	Right dorsal caudate nucleus	42	3.98	<0.001	15, 1, 26
	Left dorsal caudate nucleus	85	4.08	<0.001	-18, -4, 23
	Right ventral putamen	151	4.36	<0.001	24, 14, 2
	Left ventral putamen	*	4.32	<0.001	-27, 8, -1
Block 2-8 minus rest	Right cerebellum	54	5.31	0.013	-45, -52, -32
Block 1 minus Block 8	Right dorsal caudate nucleus	*	3.98	<0.001	18, -4, 23
	Left dorsal caudate nucleus	23	4.26	<0.001	-18, -4, 23
	Right cerebellum	293	5.17	<0.001	27, -40, -32
	Left thalamus	160	4.65	<0.001	-6, -1, 1
	Left temporal occipital fusiform cortex	173	4.62	<0.001	-39, -58, -23
	Right superior temporal gyrus	67	4.28	0.009	42, -34, 4
	Right occipital pole	57	4.21	0.014	15, -100, 10
	Left postcentral gyrus	35	4.01	0.047	-30, -19, 37
	No suprathreshold activations				

Cluster size is reported in voxels. *Q* values are reported at a significance level of $q < 0.05$ corrected for false discovery rate (FDR) at the cluster-level. *T* values are reported at the voxel level. Coordinates are reported in MNI space. Striatal regions are presented first and highlighted in each contrast. SR – stimulus-response events; FB – feedback events. *Cluster size unobtainable as peak coordinates are within a larger cluster, *q* value reported is FDR corrected at the voxel level.

Stimulus-response decisions: Block 1, Session 2. Significant activation arose in the left (*peak coordinates*: -18, -4, 23; $t = 4.08$; $q < 0.001$), and right (*peak coordinates*: 15, 1, 26; $t = 3.98$; $q < 0.001$) dorsal caudate nucleus, as well as left (*peak coordinates*: -27, 8, -1; $t = 4.32$; $q < 0.001$) and right (*peak coordinates*: 24, 14, 2; $t = 4.36$; $q < 0.001$) ventral putamen, when Block 1 decision events were contrasted with rest periods (Figure 4.7A). No significant striatal activation arose for each of Blocks 2-8 when compared with rest events at $q < 0.05$ FDR or even using a more liberal criterion of $p < 0.005$ uncorrected for multiple comparisons. Significant activation in left and right dorsal caudate nucleus arose when stimulus response events in Block 1 were contrasted with those in Block 8 of Session 2 (*peak coordinates*: -18, -4, 23; $t = 4.26$; $q < 0.001$ and *peak coordinates*: 18, -4, 23; $t = 3.98$; $q < 0.001$, respectively; Figure 4.7B and C).

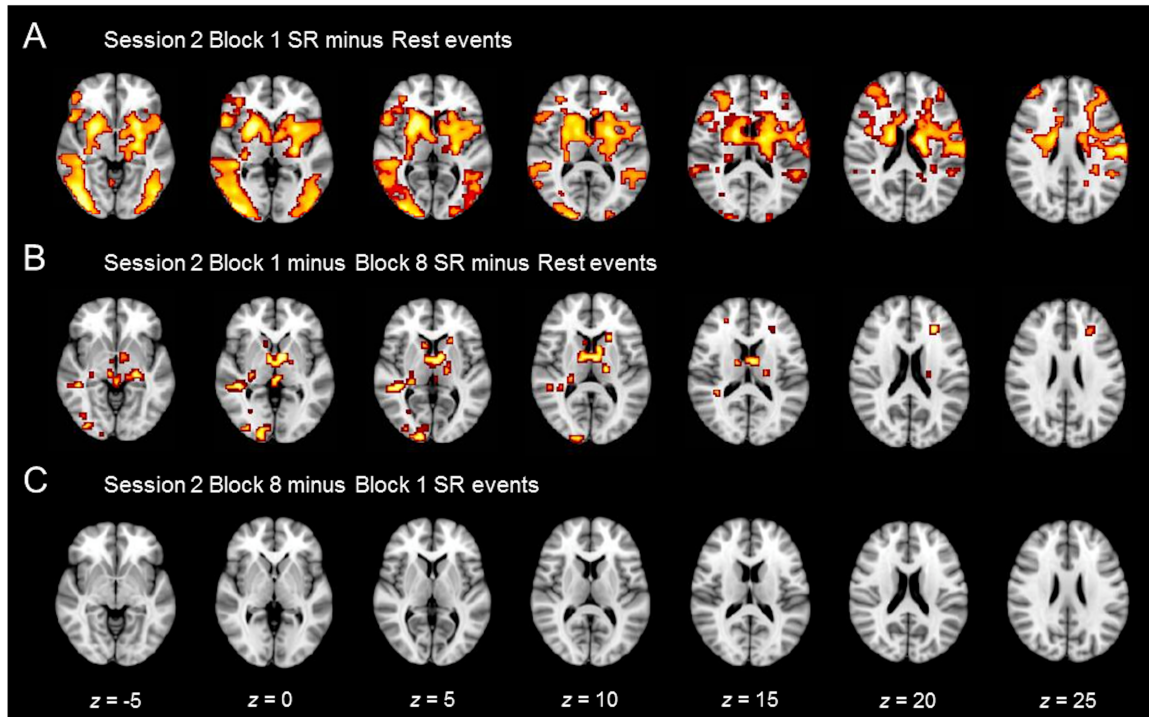


Figure 4.7 Significant activations in contrasts of interest in Session 2.

The figure shows significant activation at a threshold of $q < 0.05$ corrected for false discovery rate (FDR). In each contrast of interest, horizontal slices are presented ranging from $z = -5$ to $z = 25$, every 5 mm. **A)** BOLD signal for stimulus-response events of Block 1 of Session 2 minus rest. **B)** BOLD signal for stimulus-response events of Block 1 minus Block 8 of Session 2. **C)** BOLD signal of stimulus-response events of Blocks 8 minus Blocks 1 of Session 2. SR – stimulus-response events.

4.3.3.3 Session 3

Session 3 contrasts of interest are reported in Table 4.5.

Localization responses: There were no significant activations in any striatal regions for contrasts of facilitation (i.e., congruent minus control trials), interference (i.e., incongruent minus control trials), or incongruent and congruent vs. control trials at an FDR corrected threshold of $q < 0.05$. At a less stringent threshold of $p < 0.005$ uncorrected, however, contrasting incongruent and congruent trials (i.e., conditions in which suppression of previously-learned stimulus-identity responses were required in favour of the less-practiced location responses) with control trials (i.e., condition in which there were no previously-learned stimulus-identity responses to distract from location responses), a 271

voxel cluster in left dorsal putamen extending into dorsal caudate nucleus appeared (*peak coordinates*: -18, -13, 14; $t = 2.86$; $p < 0.003$).

Table 4.5 Significant brain activations in Session 3 contrasts of interest reported in MNI space.

Contrast	Anatomical Area	Cluster Size	t	p	x, y, z
Facilitation (Congruent minus Control)	No suprathreshold activations				
Control minus Congruent	No suprathreshold activations				
Interference (Incongruent minus Control)	No suprathreshold activations				
Control minus Incongruent	No suprathreshold activations				
Incongruent minus Congruent	No suprathreshold activations				
Congruent minus Incongruent	No suprathreshold activations				
Congruent and Incongruent minus Control	Left dorsal putamen	271	2.86	0.003	-18, -13, 14
Control minus Congruent and Incongruent	No suprathreshold activations				

Cluster size is reported in voxels. P values are reported at a significance level of $p < 0.005$ uncorrected for multiple comparisons. T values are reported at the voxel level. Coordinates are reported in MNI space. Striatal regions are presented first and highlighted in each contrast. Facilitation was calculated as mean RTs in the congruent minus control condition and interference was calculated as mean RTs in the incongruent minus control condition.

4.3.3.4 Bayesian Analysis

Beta values in the bilateral dorsal caudate nucleus ROI were extracted for stimulus-response events separately for Sessions 1, 2, and 3. These values were used in the Bayesian analysis. To rule out a role for DS in late stimulus-response learning, DS BOLD signal was predicted to attenuate, despite behavioural signs of ongoing late-stage learning, during Phase 2, Session 1, and Blocks 2-8, Session 2. Bayes' factor one-sample t -tests were conducted on the beta values extracted from the dorsal caudate nucleus ROIs in these sessions. In this Bayesian analysis, a Bayes' factor of less than 3 is considered to significantly support the null hypothesis (Dienes, 2014) that DS activation was not correlated with stimulus-response events.

Session 1 Bayes' factors: Bayes' factor one-sample t -tests were conducted separately on the average beta values for each block in Session 1. As supported in the whole brain analysis, Bayes' factors in Blocks 1-4 significantly supported the alternative hypothesis that activation in DS in these blocks is significantly greater than zero. Blocks 5-12,

however, all had a Bayes' factor of less than 3, indicating that the beta values in DS are not greater than zero, strongly supporting the null hypothesis. That is, in Session 1, DS appears to mediate response-selection responses in Phase 1 (i.e., Blocks 1-3), with values ranging from 7.2-15.4, as well as in Block 4, with a Bayes' factor of 8.5. These results strongly support the alternative hypothesis. For all subsequent blocks in Session 1, Bayes' factors were well below the cut-off of 3, with a mean Bayes' factor of 1.12 (0.09) in all blocks but one. In Block 10 only, an isolated finding, the DS Bayes' factor trended toward being greater than zero ($BF_{10} = 2.78$). Entirely, consistent with the frequency-based statistical analyses, our Bayesian analysis of these data strongly support the view that DS BOLD signal preferentially arises during blocks when response deliberation is expected based on serial order positions, and confirmed by RT, accuracy, and the variability of behaviour across trials.

Session 2 Bayes' factors: A similar Bayesian analysis was conducted on each of the eight average block beta values extracted from the DS ROI. Supporting the Session 2, whole brain analysis, only the first block was trending towards being significantly greater than zero ($BF_{10} = 2.61$). Blocks 2-8 had Bayes' factors of less than 1, with a mean Bayes' factor of 0.20 (0.01), strongly supporting the null hypothesis, that the average DS beta values are not significantly greater than zero. That is, DS is neither mediating learning or responding in these later sessions when responses were relatively effortless and therefore required less reflection.

Session 3 Bayes' factors: Similarly to the above Bayesian analyses for Sessions 1 and 2, beta values were extracted from the bilateral DS ROIs for each of the congruent, incongruent, and control regressors. Bayes' factor, one-sample *t*-tests were conducted on facilitation (i.e., congruent minus control trials) and interference (i.e., incongruent minus control trials) scores. All scores had a Bayes' factor of less than 1.5 indicating that for facilitation ($BF_{10} = 1.30$), interference ($BF_{10} = 0.46$), as well as for the sum of congruent and incongruent minus control ($BF_{10} = 0.62$), DS activity beta values are not significantly greater than zero using this analysis.

4.4 Discussion

Examining late-stage stimulus-response learning, we found that DS activity—specifically the body of dorsal caudate nucleus—correlated with deliberate decision-making rather than feedback events, replicating our main finding in Nole M. Hiebert, Vo, et al. (2014). We divided Session 1 into Phases 1 and 2, guided by the serial order of blocks and based on behavioural data. We examined Phases 1 versus 2 of Session 1, and Block 1 versus 2-8 of Session 2 separately because the concepts that DS mediates a) learning stimulus-response associations to the point of automaticity versus b) deliberate response selections, predict different patterns of DS engagement during earlier versus later trials of Session 1 and in the initial block of Session 2 compared to later blocks.

Significant DS activity occurred during stimulus-response events in Phase 1, Session 1, but not Phase 2, Session 1. These findings held whether stimulus-response events in Phase 1 and 2 were contrasted with rest periods, with feedback periods, or with one another. This is important because stimulus-response automaticity had not been achieved at the end of Session 1, attested to by improved RT and differences in BOLD signal across Phase 2, Session 1 to Session 2. Further, pairwise comparisons across blocks in Session 1, continued to reveal small but significant differences in RT throughout, though SD and accuracy had plateaued. Evidence that stimulus-response automaticity was achieved only occurred by the end of Session 2, given a) increased errors in the incongruent relative to the control conditions, b) a trend toward significant interference (i.e., incongruent minus control) in terms of RT data, and c) significant DS activation (i.e., dorsal putamen extending into dorsal caudate nucleus), in a location-based Stroop task in Session 3. If DS mediates learning to the point of automaticity, DS activation should persist until this process is complete. DS BOLD signal dropped out well before this point, demonstrating dissociation between DS BOLD signal and the progression of stimulus-response association automatization. DS activation was significantly greater for stimulus-response events in Phase 1, Session 1, relative to Phase 2, Session 1 (i.e., Blocks 7-9; 10-12). The correspondence of DS activity with stimulus-response decisions in Phase 1, when longer RTs, lower accuracy, and greater trial-by-trial variability (i.e., SD) occurred, relative to

when more stable responding occurred in Phase 2, was entirely in keeping with its proposed role in deliberate decision making.

A main aim of Session 2, and the 20-minute distractor task that occurred prior to it, was to create situations in which predictions regarding DS activation levels would differ for the competing accounts of DS's role in cognitive function. Further, Session 2 was designed to evaluate whether automaticity had been achieved by the end of Session 1. This would be suggested by an absence of change in a) behaviour (i.e., RT, SD, or accuracy) and b) BOLD signal from Phase 2, Session 1 to Session 2, despite an intervening period of distraction. As detailed above, this was not the case. Further, the distractor period was intended to re-introduce some uncertainty and hence deliberation in response-selection decisions. If DS mediates deliberate response selections, generating uncertainty was expected to cause an increase or re-engagement of DS activity initially in Session 2 (i.e., in Block 1), until participants re-familiarized themselves once more with stimulus-specific responses. Supporting the view that DS mediates deliberate, response decisions, DS BOLD signal re-emerged and correlated with stimulus-response events in Block 1 of Session 2 only. This block occurred immediately following a 20-minute, unrelated distractor task. DS BOLD signal did not correlate preferentially with stimulus-response decisions in Blocks 2-8 of Session 2 compared to rest. Further, significantly greater DS BOLD signal resulted comparing Block 1, immediately following distraction, to Block 8, at the end of Session 2.

Using fMRI in healthy controls, we can only contradict the entrenched view that DS mediates development of stimulus-response automaticity by demonstrating absence of DS BOLD signal despite behavioural evidence that stimulus-response automatization remained in progress (i.e., a null result). That is, this claim would be challenged by dissociating neural signal in DS and behavioural signs of learning. There is a, perhaps, justified bias against publishing null effects. Null effects can have multiple interpretations including the possibility that a true difference was not detected due to insensitivity of measures or related to lack of statistical power (i.e., Type II error). Further with frequentist approaches, the null and the alternative hypotheses are set up to be asymmetric with investigator control of the maximum error allowable for supporting the alternative hypothesis whereas the error associated Type II errors varies in each study based on

experimental features and power (Dienes, 2014). The application of Bayesian analysis can reduce pitfalls in dealing with negative results and interpreting null effects. Bayesian analysis treats null and alternative hypotheses symmetrically, using the data themselves to determine the relative fit to the respective models. In this way, the statistical obstacles and validity of accepting versus rejecting the null hypotheses are equated with Bayesian analysis (Dienes, 2014).

We performed Bayesian analysis on average block beta values extracted from bilateral DS, specifically the dorsal caudate nucleus ROIs. These ROIs were defined using the anatomical boundaries of the caudate nucleus above $z = 2$ mm. There was significant support for dorsal caudate nucleus BOLD greater than zero in Phase 1, Session 1, as well as in Block 4 (i.e., the first block of Phase 2), Session 1. Bayesian analysis significantly supported accepting the null hypothesis that activation of DS activation was not greater than zero in all blocks save Block 4 of Phase 2, Session 1. Frequency-based analyses revealed significant re-emergence of dorsal caudate nucleus activation in Block 1, Session 2. The Bayes' Factor only trended toward significance for Block 1, Session 2 (i.e., 2.61 with significance threshold set at 3), not fully supporting the alternative hypothesis. It is notable, however, that the mean Bayes' factors for all other blocks in Session 2 (i.e., Blocks 2-8) was 0.20. This pattern of results is entirely incompatible with the view that DS mediates late-learning to the point of automaticity and wholly supports the notion that DS underlies decisions that still require reflection

4.4.1 Supplemental Experiment 2

Based on improved RT and differences in BOLD signal from Phase 2, Session 1 to Session 2, automaticity was not achieved at the end of Session 1 let alone at the end of Phase 1, Session 1. Nonetheless, DS signal had dropped out by Phase 2 (i.e., across Blocks 5-12), Session 1. Significant DS BOLD signal was noted only in Phase 1 (i.e., Blocks 1-3, and Block 4, the latter was only revealed using Bayesian analyses), Session 1 when RT, error rates, and mean block SDs were high, suggesting deliberation. Preferential DS BOLD signal also occurred in Block 1, Session 2, following a 20-minute distractor task aimed at re-introducing uncertainty and some consideration of response selection decisions. Phase

1, Session 1 constituted only 9 presentations of each stimulus, which referring to the larger literature would be insufficient to support the development of automatic stimulus-specific responding (Foerde, Knowlton, & Poldrack, 2006; Helie et al., 2010; C. M. MacLeod & Dunbar, 1988; Myers et al., 2003; R. A. Poldrack et al., 2005; Shiffrin & Schneider, 1977; Shohamy & Wagner, 2008; Wachter, Lungu, Liu, Willingham, & Ashe, 2009). Nonetheless, to be entirely certain of our interpretations of the Main Experiment, we conducted Experiment 2 (Methods and Results presented in (2.6.1)). In this behavioural experiment, we included a location Stroop task immediately after Phase 1, Session 1 (i.e., Session 3A) as well as at the end of Session 2 (i.e., Session 3B), to directly rule out the possibility that stimulus-response automaticity had been achieved after Phase 1.

Performance in Sessions 1 and 2 of Experiment 2 entirely replicated behavioural findings in our Main Experiment (i.e., compare Figures 2.5 and Figure 2.9). Significant interference in location responses using RT or accuracy did not occur in the incongruent relative to the control condition in Session 3A. Similarly, there was not significant RT or accuracy facilitation in the congruent relative to the control condition in Session 3A. Consequently, there was no evidence that stimulus-specific responses had achieved automatic status at the conclusion of Phase 1, Session 1, based on performance of a modified location Stroop task in Session 3A. There was a trend toward slower RTs in Block 1, Session 2, relative to Block 12, Session 1, replicating the finding in our Main Experiment that stimulus-response automaticity was not achieved by the end of Session 1.

In contrast, significant interference in terms of RT occurred during Session 3B, after stimulus-response associations had been trained in Session 1 (i.e., twelve blocks), and Session 2 (i.e., eight blocks), for incongruent relative to control trials. This suggests that stimulus-response automaticity was achieved by the end of Session 2, entirely consistent with our findings in the Main Experiment.

The results in Experiment 2, inform our interpretation of the fMRI findings in the Main Experiment. Taken together, the results favour the view that DS activation correlated with stimulus-response events in Phase 1, Session 1, when an element of deliberation remained, because this region has a role in decision making, as has been suggested by others as well

(Ali et al., 2010; R. Cools & D'Esposito, 2011; Daniel et al., 2010; P. A. MacDonald et al., 2011; Ohira et al., 2010)

4.4.2 Summary

Automaticity is variously defined as reflecting stimulus-specific responses that a) persist even when feedback is omitted or is reversed, generalizing across situations (Myers et al., 2003; Shohamy & Wagner, 2008), b) are unaffected by distracting information or tasks (Foerde et al., 2006), and c) interfere with enacting new incongruent responses (C. M. MacLeod & Dunbar, 1988). DS has been implicated in the development of automatic stimulus-specific responses (Ashby et al., 2010; Tricomi et al., 2009; Yin & Knowlton, 2006). DS has also been ascribed a role in decision making when deliberation is required (Ali et al., 2010; R. Cools & D'Esposito, 2011; Daniel et al., 2010; DeGutis & D'Esposito, 2007; P. A. MacDonald et al., 2011; Ohira et al., 2010; Robertson et al., 2015). Our results refute a role for DS in late-stage, stimulus-response learning and automatization, and rather are entirely consistent with the view that DS mediates deliberate decision making.

In this experiment, significant DS activity— particularly the body region of the dorsal caudate nucleus— occurred only during stimulus-response, and not feedback events, replicating our main finding in Hiebert et al., (2014b) suggesting that DS mediates response decisions and not learning from feedback. Further supporting a role for DS in mediating decisions, DS was significant in Phase 1, Session 1, when longer RTs, lower accuracy, and greater trial-by-trial variability suggested a degree of indecision and hence deliberation was required. Session 2 was performed following a 20-minute distractor task that aimed to re-introduce some uncertainty in response-selection decisions. This provided a further test of the hypothesis that DS mediates decision making when choosing among response alternatives demands some contemplation of options. As we had predicted, we observed a transient re-emergence of DS activation, correlating with the decision-making events in Block 1, Session 2, immediately following distraction. In contrast, during Phase 2, Session 1, and Blocks 2-8 of Session 2, stimulus-response decisions did not correlate significantly with DS BOLD signal. Further, Bayesian analysis supported these null results in all but Block 4 (i.e., the first block) of Phase 2, Session 1. In our Main Experiment, stimulus-

response automaticity had not been achieved at the conclusion of Session 1 based on the evidence that RTs and BOLD signal differed from Block 12, Session 1 and Block 1, Session 2 and the additional finding that pairwise *t*-tests of RT for individual blocks across Session 1 continued to shorten slightly across blocks. Stimulus-response associations were over-learned to the point of automaticity at the conclusion of Session 2, supported by the finding that stimulus-response associations learned in Session 1 and reinforced in Session 2 facilitated congruent and interfered with incongruent location responses in a modified location Stroop task. In Experiment 2, we sought direct evidence that Phase 1, Session 1 was not sufficient to promote development of stimulus-response automaticity, using our location Stroop task (See 2.6). Experiment 2 revealed that stimulus-response automaticity was not achieved following Blocks 1-3, Session 1 (i.e., Phase 1) after only 9 presentations of each stimulus. The fact that DS activation attenuated after Phase 1, Session 1, before automaticity was achieved, in the Main Experiment is therefore wholly inconsistent with the contention that DS mediates late-stage, stimulus-response learning to the point of automaticity (Ashby et al., 2007; Balleine & O'Doherty, 2010; Yin & Knowlton, 2006). There was a clear dissociation between DS BOLD signal and behavioural evidence of late-stage, stimulus-response association automatization.

In contrasts where DS activation emerged significantly, cortical regions previously implicated in decision making and categorization judgments were also revealed. These included occipital regions of the fusiform gyrus that have been implicated in decision making, specifically in motor planning and execution (Tosoni, Guidotti, Del Gratta, Committeri, & Sestieri, 2016), as well as the occipital pole and lateral occipital cortex that are both implicated in object recognition (Vernon, Gouws, Lawrence, Wade, & Morland, 2016). Object recognition is a required step toward enacting stimulus-specific response selections. The right inferior frontal gyrus has been shown to implement and reprogramme action plans (Stock, Steenbergen, Colzato, & Beste, 2016). Many of the brain regions that were significantly activated along with DS during response-selection events are reciprocally connected with the dorsal caudate nucleus, the body specifically, such as the precentral, postcentral, inferior, and fusiform gyri (Robinson et al., 2012; Tziortzi et al., 2014). These results highlight the fact that, whereas the DS does not function in isolation, it plays a key, central role in performing response-related decisions.

4.4.3 DS in Stimulus-Response Learning versus Decision Making

The claim that DS mediates learning is well-entrenched (Ashby et al., 2007; Ashby et al., 2010; Balleine et al., 2009; Brovelli et al., 2011; O'Doherty et al., 2004; Yin & Knowlton, 2006). Challenges to this notion are accruing, however (Atallah et al., 2007; Exner et al., 2002; A. A. MacDonald, Monchi, et al., 2013; Vo et al., 2014). In a previous experiment, we investigated DS's role in *early* stimulus-response learning. We found that DS activity, particularly the head of dorsal caudate nucleus, correlated with stimulus-response decisions and enactment, not with feedback processing, the point at which early, stimulus-response associations are learned (Nole M. Hiebert, Vo, et al., 2014). In that experiment, DS activity did not correlate with response decisions in the first half of our session, before response tendencies had developed. DS activity emerged and correlated significantly with stimulus-response decisions in later stages of stimulus-response learning. At these later stages when DS activity correlated with stimulus-response events, the learning curve was shallower and therefore DS did not seem to be tracking learning behaviour *per se*. Further, and quite convincing that DS does not mediate early, stimulus-response learning via feedback, DS preferentially correlated with stimulus-response decision events in Session 2, when feedback was omitted and hence further feedback-based learning was precluded. In Session 2, however, decision accuracy remained imperfect (i.e., mean 92%), and RTs (i.e., mean 696 ms) suggested some deliberation was required. That is, DS activity arose when stimulus-specific responses were not overlearned and still required a degree of deliberation in this session of our previous experiment. We argued that DS is erroneously implicated in stimulus-response learning because it mediates aspects of decision making, and most stimulus-response learning studies combine decision and learning processes. This confound exists at the behavioural level in that expression of learning typically depends upon intact decision-making abilities. In neuroimaging studies, neural activation associated with learning and decision processes are frequently merged into a single *learning* event. Though our previous finding seriously challenged the premise that DS mediates early stimulus-response learning, we could not comment on the DS's role in late-stage learning, particularly in stimulus-response automaticity that occurs through repeated experience of stimulus-response associations and does not necessarily depend upon

feedback. The view that DS mediates late learning is also prevalent (Ashby et al., 2010; Balleine et al., 2009; Ruge & Wolfensteller, 2013; Tricomi et al., 2009) and this served as the impetus for the Main Experiment.

Extending our previous investigation (Nole M. Hiebert, Vo, et al., 2014), here we examined DS's role in late-stage learning versus decision making. Our results were entirely consistent with the view that DS mediates decisions when a degree of deliberation is required (Session 1, Phase 1; Session 2, Block 1), consistent with our previous conclusions regarding DS's role in an early-learning experiment (Nole M. Hiebert, Vo, et al., 2014). That DS activity attenuated *before* automaticity had been achieved is inconsistent with the view that it mediates late-stage stimulus-response learning (Balleine & O'Doherty, 2010; Helie et al., 2010; Liljeholm & O'Doherty, 2012; Macpherson, Morita, & Hikida, 2014; Soto et al., 2013; Voorn, Vanderschuren, Groenewegen, Robbins, & Pennartz, 2004; Yin & Knowlton, 2006). If the role of DS is to learn stimulus-response associations and to train cortical-cortical connections to the point of automaticity, DS activity should have persisted into Session 2, given that this learning process had not reached completion based on differences in RT and BOLD signal from Session 1 to Session 2 (Ashby, et al., 2007). The current results are therefore at odds with the SPEED model ascribing DS a role in mediating automaticity (Ashby et al., 2007; Helie et al., 2010) as well as with the theory that DS not only mediates stimulus-response habit learning but also underlies responding that is habitual (Balleine & O'Doherty, 2010; Everitt & Robbins, 2005).

The finding that DS activity for stimulus-response events attenuates prior to the development of automatic responding has been shown convincingly by others as well (Wu, et al., 2004; Waldschmidt and Ashby, 2011; Soto et al., 2013). de Wit, Barker, Dickinson, and Cools (2011) used an instrumental conflict task, where participants first learned simple biconditional associations in a goal-directed or habit fashion, and later performed decisions where select outcomes were devalued. Patients with PD, tested in the OFF or ON dopaminergic medication states, scored similarly to controls in the outcome-devalued stage of the experiment with respect to both the goal-directed and habit learned associations. In PD, DS is significantly dopamine depleted and hence DS functions a significantly impaired in the off state and are improved by dopaminergic therapy. These findings, therefore

suggest that DS does not mediate the development of automaticity, or interestingly even goal-directed learning in this task (de Wit et al., 2011).

More consistent with our current results, as well as with our previous findings (Nole M. Hiebert, Vo, et al., 2014), DS seems to be implicated in decision making only once stimulus-response tendencies begin to develop, when a degree of deliberation remains, but before responses are enacted with little reflection or automatically (Figure 2.7). These results integrate with a growing literature linking DS to decision making (Atallah et al., 2007; Grahn, Parkinson, & Owen, 2008), particularly the body of the caudate nucleus. as we have shown here, (Cincotta & Seger, 2007; Little, Shin, Sisco, & Thulborn, 2006; Seger, Peterson, Cincotta, Lopez-Paniagua, & Anderson, 2010), and especially when deliberation, as well as cognitive control or flexibility processes are required (R. Cools & D'Esposito, 2011; Robertson et al., 2015). In neuroimaging studies, DS activity correlates with degree of category (Daniel et al., 2010), response-reward (Ohira et al., 2010), and stimulus-response (Ali et al., 2010; P. A. MacDonald et al., 2011) uncertainty. Further, investigations in patients with DS lesions and in PD patients reveal more significant impairments for decisions requiring greater deliberation and in some cases *superior performance* relative to healthy controls for choosing *more* automatic responses (Benke et al., 2003; Cameron et al., 2010; R. Cools et al., 2006; Roshan Cools et al., 2010; Hood et al., 2007; P. A. MacDonald et al., 2011; Thoma et al., 2008). Finally, in neuroimaging studies that utilize the Stroop task, a robust paradigm that examines cognitive control (C. M. MacLeod & MacDonald, 2000) resolving response conflict and inhibiting pre-potent responses in the incongruent condition frequently implicate DS (Ali et al., 2010; Coderre & van Heuven, 2013; Robertson et al., 2015). These findings are at odds with any theory that ascribes a role to DS in habit learning or habitual responding.

4.4.4 Role of the Striatum in Stimulus-Response Learning and Decision Making

Figure 4.8 presents our theorized patterns of DS and VS engagement for stimulus-response versus feedback events separately, following the course from early- to late-stage learning and decision making, based on our previous (Nole M. Hiebert, Vo, et al., 2014) and current

results. In Nole M. Hiebert, Vo, et al. (2014), stimulus-response learning in Session 1 was divided in half. The first half revealed a much steeper slope of stimulus-response learning via feedback than the second. The average percent accuracy achieved after the first half of Session 1 in Nole M. Hiebert, Vo, et al. (2014) was 57%. The average percent accuracy at the end of the second half of Session 1 (i.e., final learning score) was 93%. In the Main Experiment, after a period of explicit study of stimulus-response associations, the percent accuracy of the first block of trials in Session 1 was 94%. Session 1 of the current study was divided into Phases 1 (Blocks 1-3) and 2 (Blocks 4-12) based on behavioural patterns of accuracy, RT, and inter-trial variability. The average percent accuracy and RT achieved at the end of Phase 1 were 97% and 746 ms and at the end of Phase 2 were 98% and 694 ms, respectively.

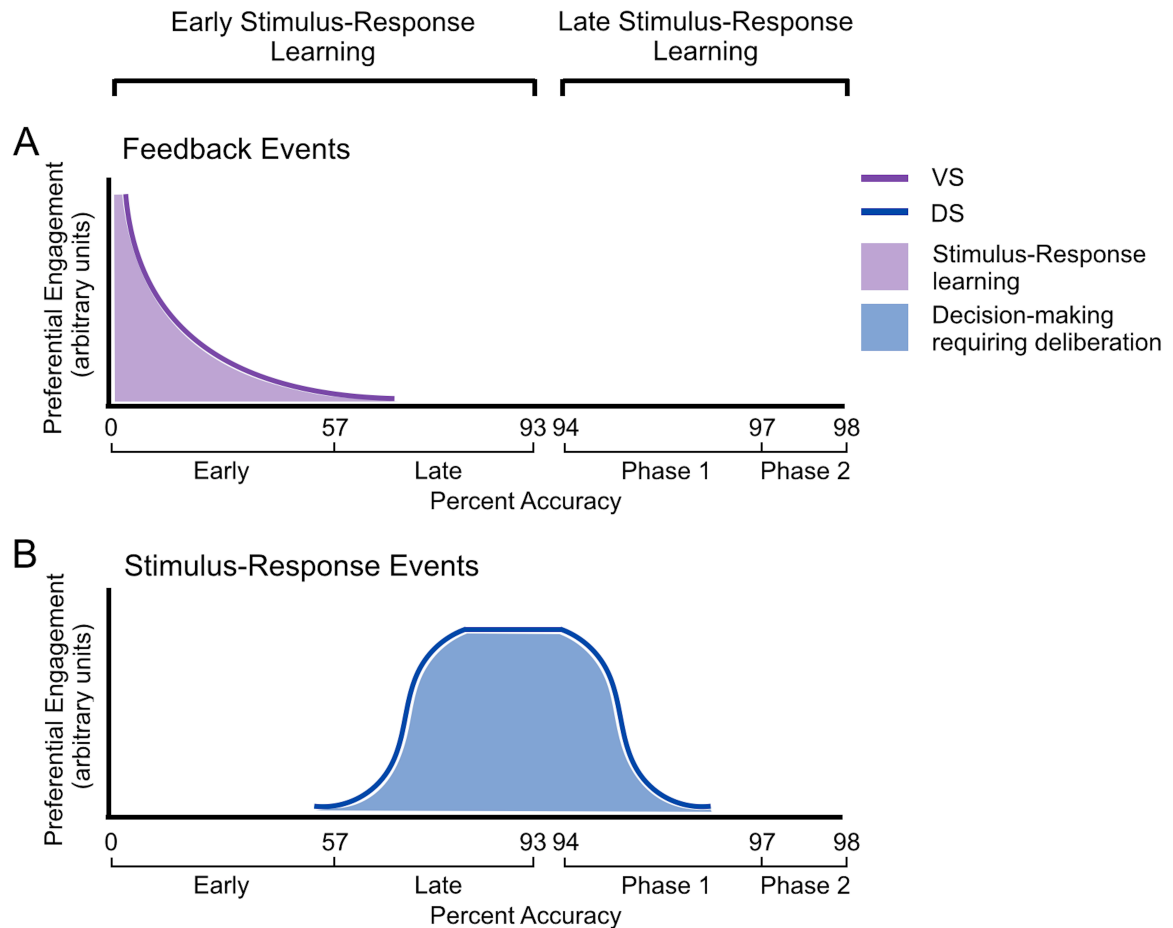


Figure 4.8 Roles of DS and VS in early and late stimulus-response learning as supported by our findings in N. M. Hiebert et al. (2014) and the Main Experiment of the current study.

Graphs presented above illustrate preferential patterns of DS and VS activation for stimulus-response events versus feedback separately, following the course of learning from early to late stage. This is not actual data and the amplitude and shape of curves reflect our theoretical interpretations of our results. We present Session 1, of Nole M. Hiebert, Vo, et al. (2014), divided in half. Average percent accuracy achieved after the first half of Session 1 was 57%. The average percent accuracy for Session 1 final learning, was 93%. For the current study, percent accuracy for Block 1, Session 1 was 94%. Session 1 was divided into Phase 1 (Blocks 1-3) and 2 (Blocks 4-12). The average percent accuracy achieved at the end of Phase 1 was 97% and at the end of Phase 2 was 98%. **A) Activation patterns during feedback events.** VS activity was noted significantly only in the first half of Session 1 (Nole M. Hiebert, Vo, et al., 2014) VS was not significantly engaged during the feedback events in the Main Experiment. **B) Activation patterns during stimulus-response events.** DS activity was noted significantly only during the second half of Session 1 and Session 2 (Nole M. Hiebert, Vo, et al., 2014) when stimulus-response associations were learned but still required deliberation. In the Main Experiment, DS was only significant in Phase 1, Session 1 when response selections were learned but still required deliberation based on accuracy and RT. Preferential DS activity was not noted

relative to rest, feedback, or Phase 1 stimulus-response events, for stimulus-response events during Phase 2 of Session 1 and for the bulk of Session 2.

DS was preferentially engaged during stimulus-response events in both experiments (Figure 4.8B). DS activity peaked towards the end of the learning phase in Nole M. Hiebert, Vo, et al. (2014) when stimulus-response associations were beginning to form but when response selections were still somewhat uncertain (i.e., > 57% accuracy). In the current study, DS activity occurred early once response selections were learned but still required deliberation based on accuracy and RT (i.e., < 97% accuracy). DS activity did not correlate preferentially with stimulus-response events during Phase 2 of Session 1 of the Main Experiment in which accuracy was above 97% and RTs were quite short. We conceptualize that responses during Phase 2 of Session 1 required much less consideration though they had not yet achieved automaticity based on our objective measures. These results together suggest that DS neither mediates early, feedback-based learning, nor late-stage stimulus-response automaticity. Instead, these results integrate with a growing literature implicating DS in decision making (Atallah et al., 2007; Grahn et al., 2008), particularly when deliberation is required (R. Cools & D'Esposito, 2011).

In contrast, VS was preferentially engaged during feedback events (Figure 4.8A) in Nole M. Hiebert, Vo, et al. (2014), peaking in the first half of Session 1, when the slope of learning was steepest. VS BOLD signal for feedback events was not significantly different relative to rest or stimulus-response events in the second half of Session 1 in Nole M. Hiebert, Vo, et al. (2014), when slope of behavioural change indicated that learning had decreased. Consistent with this pattern, VS was not significantly engaged during the feedback events in Session 1 of the current study, which focused on late learning. Early stimulus-response association learning had already occurred prior even to Block 1, Session 1 in the Main Experiment, due to an explicit learning session that preceded the fMRI portion of this study, intended as a short-cut to later learning, making feedback much less informative. Our results integrate with an emerging literature suggesting that VS mediates many forms of initial/early learning both with and without the provision of feedback, including reward learning (Camara, Rodriguez-Fornells, & Munte, 2008; A. A. MacDonald, Monchi, et al., 2013), stimulus-stimulus learning (P. A. MacDonald et al.,

2011), motor learning (Feigin et al., 2003), sequence learning (Ghilardi et al., 2007), category learning (Hampshire et al., 2016; Shohamy, Myers, Gekhman, Sage, & Gluck, 2006), and list learning (A. A. MacDonald, Seergobin, et al., 2013).

4.4.5 Conclusions

The striatum is increasingly implicated in cognitive functions (P. A. MacDonald, Ganjavi, Collins, Evans, & Karama, 2014). We found that DS activity correlates only with decisions and response selections requiring deliberation but not with late-stage, stimulus-response association learning. Our results challenge the notion that the DS underlies the development of automaticity, integrating rather with a growing literature suggesting that DS—particularly the caudate nucleus—mediates decision making (Cincotta & Seger, 2007; Little et al., 2006; Seger et al., 2010) when an element of deliberation is required (Atallah et al., 2007; Grahm et al., 2008; Nole M. Hiebert, Vo, et al., 2014; Jessup & O'Doherty, 2011; A. A. MacDonald et al., 2014; McDonald & Hong, 2004; Postle & D'Esposito, 1999; Smittenaar et al., 2012).

4.5 Acknowledgements

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4.6 Supplemental Material: Experiment 2

The aim of Experiment 2 was to objectively measure whether stimulus-response automaticity could be achieved following Phase 1 of Session 1, using our modified location Stroop task, which was shown to be a sensitive measure of stimulus-response automaticity in Session 3 of the Main Experiment. The experimental protocol was identical to the Main Experiment, except that no fMRI measures were acquired and automaticity was assessed immediately after Phase 1 (i.e., Blocks 1-3) of Session 1 as well as at the end of Session 2

using a modified Stroop task. In Experiment 2, we refer to this new block of location-Stroop trials as Session 3A and the block of location-Stroop trials occurring after Sessions 1 (i.e., 12 blocks) and 2 (i.e., 8 blocks) as Session 3B.

4.6.1 Materials and Methods

4.6.1.1 Participants

Fifteen healthy, young adults participated in this experiment (5 males, 10 females). Subjects had a mean (SEM) age and level of education of 22.47 (0.50) and 16.33 (0.42) years, respectively. Participants abusing prescription or illicit drugs, alcohol, or taking cognitive-enhancing medications including methylphenidate were excluded from participating in the experiment. The Health Sciences Research Ethics Board of the University of Western Ontario approved this study. All participants provided informed, written consent, according to the Declaration of Helsinki (2013).

4.6.1.2 Procedures

Experiment 2 was identical to the Main Experiment in nearly every respect. All participants first learned explicitly to associate six abstract images with one of two button-press responses prior to learning the associations implicitly in the presence (i.e., Session 1) and absence (i.e., Session 2) of feedback. There was again a 20-minute distractor task performed between Sessions 1 and 2. Session 3B was the final session in the experiment and was identical to Session 3 in the Main Experiment. The stimuli, responses, trial number, and trial parameters were identical to what was described previously. The only difference in Experiment 2 was that following Phase 1 (i.e., Blocks 1-3), Session 1 and before Phase 2 (i.e., Blocks 4-12), Session 1, participants performed Session 3A, a modified Stroop task identical in all respects to Session 3 of the Main Experiment (See Figure 4.2A and B).

All sessions of Experiment 2 were performed using a 14.0" widescreen laptop (Lenovo T420; Lenovo, Morrisville, North Carolina, USA) running a resolution of 1600 × 900 on

the Windows 7 operating system. The screen was placed at a distance of 50 cm in front of the participant and angled for optimal viewing.

4.6.1.3 Behavioural Data Analysis

An identical set of analyses was conducted on the Session 1 and 2 behavioural data. To reiterate, changes in mean block RT, SD of RTs across blocks, and accuracy across Sessions 1 and 2 were analyzed using single-factor repeated measures ANOVAs with block (Session 1: 12 blocks; Session 2: 8 blocks) as the within-subject variable. RT was the time between the onset of the abstract image and the button press by the participant measured in ms. The number of correct “right” and “left” button-press responses recorded after each block was our estimate of accuracy. In addition, *t*-tests were run on RT and accuracy data obtained in the last block of Session 1 and the first block of Session 2 to assess forgetting during the distraction period.

Three conditions—congruent, incongruent, and control—were again created in Sessions 3A and B. Matching the Main Experiment, Sessions 3A and 3B each consisted of 48 congruent, 48 incongruent, and 48 control trials that occurred in random order. All old and new stimuli appeared equally often left and right of centre. RTs were measured from the onset of the image until the button-press response in ms. The control condition provided a baseline measure of accuracy and latency for providing a location response. As in the Main Experiment, facilitation was calculated as mean RTs in the congruent condition minus those in the control condition and interference was calculated as mean RTs in the incongruent condition minus those in the control condition. The incongruent minus congruent contrast was also completed to examine differences between incongruent and congruent trials. One sample *t*-tests were run on facilitation and interference scores to assess if they were significantly different from zero. Paired *t*-tests were performed on error rates between congruent and control trials, and incongruent and control trials. Scores were assessed separately in Session 3A and Session 3B to investigate whether the stimulus-response associations had been learned to the point that they were automatic after Phase 1 of Session 1 (i.e., Session 3A) or after completing both Sessions 1 and 2 (i.e., Session 3B).

4.6.2 Results

4.6.2.1 Behavioural Results

Behavioural results for Sessions 1 and 2 of Experiment 2 are presented in Table 4.6 and Figure 4.9. Results of Session 3 are presented in Table 4.7 and Figure 4.10.

4.6.2.1.1 Session 1

Results for Session 1 are shown with Phases 1 and 2 combined to illustrate the overall trends in RT, SD, and accuracy. The mean RT, SD, and accuracy across Session 1 are shown in Figure 4.9A – C respectively. Mauchly's test was significant, indicating the assumption of sphericity was violated ($p < 0.001$). Therefore, degrees of freedom were corrected using the Greenhouse-Geisser Epsilon for RT, SD, and accuracy single-factor repeated measures ANOVAs.

Table 4.6 Significant pairwise comparisons for RT, SD, and accuracy differences by block in Session 1 of Experiment 2.

Block A	Block B	RT		SD		Accuracy	
		<i>t</i> stat	<i>p</i> value	<i>t</i> stat	<i>p</i> value	<i>t</i> stat	<i>p</i> value
1	2	3.79	0.001	3.57	0.004	-	-
	3	>3.79	<0.001	5.12	<0.001	2.01	0.032
	4	>3.79	<0.001	4.97	<0.001	-	-
	5	>3.79	<0.001	4.88	<0.001	2.62	0.010
	6	>3.79	<0.001	4.61	<0.001	2.10	0.027
	7	>3.79	<0.001	5.00	<0.001	1.94	0.036
	8	>3.79	<0.001	5.82	<0.001	2.62	0.010
	9	>3.79	<0.001	6.34	<0.001	2.35	0.017
	10	>3.79	<0.001	5.47	<0.001	1.93	0.037
	11	>3.79	<0.001	6.37	<0.001	2.62	0.010
	12	>3.79	<0.001	5.42	<0.001	1.98	0.034
2	4	3.79	0.001	-	-	-	-
	5	2.74	0.008	-	-	-	-
	7	3.09	0.004	-	-	-	-
	8	>3.79	<0.001	-	-	-	-
	9	>3.79	<0.001	2.77	0.018	-	-
	10	>3.79	<0.001	-	-	-	-
	11	>3.79	<0.001	2.79	0.017	-	-
3	12	>3.79	<0.001	-	-	-	-
	4	1.85	0.043	-	-	-	-
	5	1.79	0.047	-	-	-	-
	8	2.19	0.023	-	-	-	-
	9	2.98	0.005	-	-	-	-
	10	2.26	0.020	-	-	-	-

	11	>3.79	<0.001	-	-	-	-
	12	3.79	0.001	-	-	-	-
4	11	3.23	0.003	-	-	1.99	0.033
	12	2.32	0.018	-	-	-	-
7	11	2.12	0.026	-	-	-	-
	12	1.92	0.038	-	-	-	-
8	9	1.77	0.049	-	-	-	-
	11	2.01	0.032	-	-	-	-

Only significant ($p < 0.05$) comparisons are reported. The left column labelled Block A lists the blocks that differ significantly from blocks listed in Block B. RT – response time, SD – standard deviation.

RTs were examined and revealed a main effect of block, $F_{(3, 47)} = 19.94$, $MSE = 34593.50$, $p < 0.001$. Deconstructing this effect using pairwise comparisons revealed significant RT differences between Blocks 1, 2, 3, 4, 7, and 8 versus other subsequent blocks (see Table 4.6 and Figure 4.9A for specific significant comparisons). No significant differences arose between Block 5, and 9-12 and other subsequent blocks. Mean RTs decreased from 1100 ms in Block 1 to 679 ms in Block 12.

For SDs of RTs across blocks, a main effect of block was revealed, $F_{(3, 36)} = 5.72$, $MSE = 45301$, $p < 0.001$ with significant differences between Blocks 1 and 2 versus later blocks (See Table 4.6 and Figure 4.9B). Mean SDs decreased from 372 ms in Block 1 to 167 in Block 12.

The single factor repeated measures ANOVA for accuracy revealed a significant main effect of Block, $F_{(4, 54)} = 2.96$, $MSE = 37.36$, $p = 0.029$. This was explored further using pairwise comparisons (results presented in Table 4.1 and Figure 4.9C). Significant differences existed between Blocks 1 and 4 versus other subsequent blocks in Session 1. No significant differences arose between blocks later than 4 with one another. The average Block 1 score was 93.70%, which increased to 98.15% in Block 12.

There was a trend in the RTs in the last block of Session 1 relative to those in the first block of Session 2 ($t = 1.36$, $p = 0.097$), with slower responding in Block 1, Session 2 than in Block 12, Session 1. This replicates our finding that stimulus-response automaticity had not been achieved at the end of Session 1 in the Main Experiment. Accuracy in the last block of Session 1 was not significantly different from accuracy in the first block of Session 2 ($t = -0.76$, $p = 0.77$).

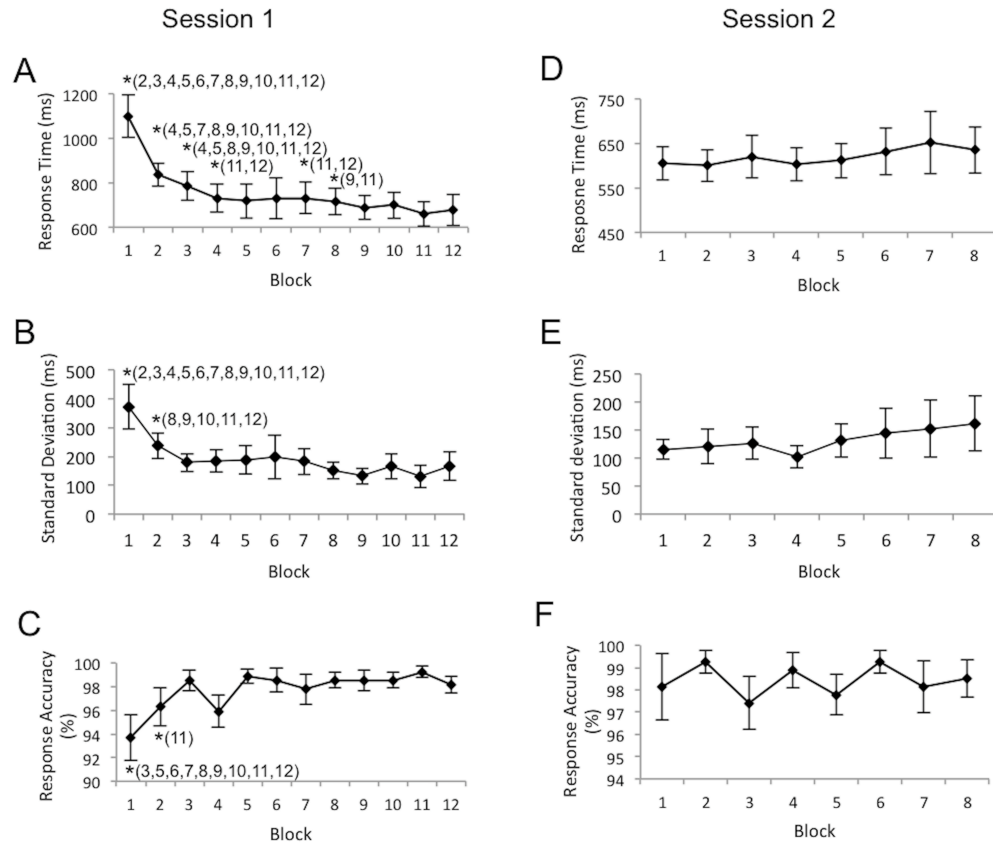


Figure 4.9 Mean response times, standard deviations, and accuracy across Sessions 1 and 2 of Experiment 2.

A) Mean response times (ms) in each block in Session 1. **B)** Mean standard deviation (ms) in each block in Session 1. **C)** Mean response accuracy (%) in each block in Session 1. Session 1 was completed as two separate phases but are presented continuously to illustrate the changes in RT and accuracy. Phase 1 consisted of Blocks 1-3 and Phase 2 was composed of Blocks 4-12. **D)** Mean response time (ms) in each block in Session 2. **E)** Mean standard deviation (ms) in each block in Session 2. **F)** Mean response accuracy (%) in each block in Session 2. Error bars represent standard error of the mean. Response time was measured from the onset of the abstract image to the button-press response made by the participant. Response accuracy is a percentage measure of the number of correct button-press responses in a block relative to total number of trials in the block. Significant differences ($p < 0.05$) are indicated with an asterisk (*) and numbers listed next to the asterisk indicate the blocks from which each block differs significantly.

4.6.2.1.2 Session 2

Mean RT, SD, and accuracy across Session 2 are presented in Table 4.6 and Figures 4.9D–F, respectively. As in Session 1, single factor repeated measures ANOVAs were run to

investigate differences across Session 2. There were no significant differences across blocks for RT ($F < 1$), SD ($F < 1$), or response accuracy ($F < 1$).

4.6.2.1.3 Sessions 3A and B

Results for Sessions 3A and B are presented in Figure 4.10 and Table 4.8. To reiterate, Session 3A was completed immediately after Phase 1, Session 1 to investigate whether automatic responses had developed following Blocks 1-3, Session 1. The error rate was 3.29%. Table 4.8 presents the mean RTs and error rates in each the congruent, incongruent, and control conditions.

Table 4.8 Mean response times and error rates for the congruent, incongruent, and control conditions in Sessions 3A and B in Experiment 2.

Condition	Session 3A		Session 3B	
	Response Time (ms)	Error Rate (%)	Response Time (ms)	Error Rate (%)
Congruent	409.45 (25.07)	3.19 (0.45)	393.44 (19.48)	0.28 (0.28)
Incongruent	403.02 (26.05)	3.75 (0.77)	402.37 (20.79)	0.28 (0.19)
Control	424.13 (32.54)	2.92 (0.34)	390.13 (18.87)	0.00 (0.00)

Mean (SEM) response times (ms) and error rates (%) are presented separately for Session 3A and B. Session 3A was completed immediately after Phase 1 of Session 1. Session 3B occurred after Session 2 was completed. In the congruent condition, an image appeared in a location that was consistent with the learned left or right button-press response. In the incongruent condition, a stimulus appeared in a location that was inconsistent with the learned left or right button-press response. In the control condition, six new images that were not previously presented in the experiment appeared to the left or right of centre.

Paired t -tests were performed on error rates between congruent and control, and incongruent and control, trials. One sample t -tests were performed on average facilitation and interference difference scores (Figure 2.10A). There were no significant differences in terms of errors between congruent and control ($t = -0.163$, $p = 0.563$), and incongruent and control ($t = -0.143$, $p = 0.612$). Facilitation ($t = -1.66$, $p = 0.119$) scores did not differ significantly from zero in terms of RTs. The incongruent minus control difference score was significant ($t = -2.65$, $p = 0.019$). However, the mean interference score was -21.11 ms indicating faster responding for familiar yet incongruent items relative to novel control symbols (Figure 4.10A).

Session 3B was completed after 12 blocks of trials in Session 1 and eight blocks of trials in Session 2. The error rate was low and similar to Session 3 of the Main Experiment (average incorrect responses: 0.19%). Table 2.7 presents the mean RTs and error rates in each the congruent, incongruent, and control conditions of Session 3B. Paired t -tests were performed on error rates between congruent and control, and incongruent and control trials. There were no significant differences in terms of errors between congruent and control ($t = 1.00$, $p = 0.334$), and incongruent and control ($t = 1.47$, $p = 0.164$). One sample t -tests were performed on average facilitation and interference difference scores based on RT, as had been completed previously (Figure 2.10B). Significant interference ($t = 3.00$, $p = 0.010$) occurred. Facilitation scores (i.e., congruent-control) did not differ significantly from zero ($t = 0.93$, $p = 0.368$).

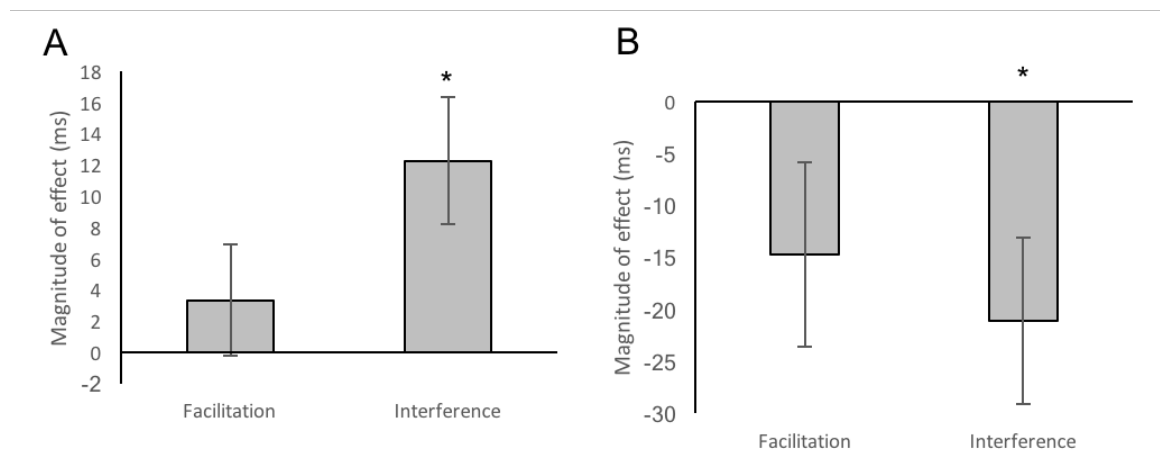


Figure 4.10 Mean facilitation and interference difference scores in Sessions 3A and B of Experiment 2.

A) Mean (SEM) facilitation and interference difference scores for Session 3A. **B)** Mean (SEM) facilitation and interference difference scores for Session 3B. Session 3A was completed immediately following Phase 1 of Session 1 and Session 3B occurred after Session 2. Facilitation was calculated as mean RTs in the congruent minus control condition and interference was calculated as mean RTs in the incongruent minus control condition. Again, in the congruent condition stimuli were presented in the location that was consistent with the learned left or right button-press response learned in earlier sessions. On incongruent trials, stimuli were presented in the location that was inconsistent with the left or right button-press response learned in earlier sessions. The control condition consisted of new images that the participant had not previously associated with a right or left button-press response. * $p < 0.05$.

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Chapter 5

5 General Discussion

In three separate experiments, using fMRI, we investigated the role of the striatum in both early and late stimulus-response learning in patients with PD, patients with OCD, and in healthy participants. In Chapter 2, in patients with PD, we found that dopaminergic therapy *improved* response accuracy related to *enhanced* DS BOLD signal. In contrast, exogenous dopamine *decreased* the efficiency of stimulus-response learning, with corresponding *attenuation* of VS activity. These results support the contention that DS mediates decision making and not early, stimulus-response learning whereas VTA-innervated VS supports stimulus-response association learning. Combining PD, fMRI, and dopaminergic therapy that *induces* changes in a) behaviour and b) correspondingly in BOLD signal, allows greater confidence in suggesting that dopamine-mediated neural changes *produce* behavioural improvements and impairments. In Chapter 3, patients with OCD evidenced impaired stimulus-specific response decisions and stimulus-response learning efficiency. Correspondingly, task-relevant DS activity during Stimulus-Response Decision Events and VS activity in Feedback Events were reduced. Lastly in Chapter 4, we demonstrated that DS does not mediate late-stage habit learning toward automaticity but rather underlies deliberative response selections.

5.1 The role of DS in stimulus-response learning

There exists a rift in the literature regarding DS' role in learning versus decision-making. There is a large literature implicating DS as a learning region, mediating both early, goal-directed learning as well as habit formation (Balleine & O'Doherty, 2010; Fouragnan, Retzler, & Philiastides, 2018; Hart, Leung, & Balleine, 2013; Salmi, Nyberg, & Laine, 2018). On the other side of the chasm, there is a competing literature supporting a role in decision making. Few studies acknowledge these contradictory functions ascribed to DS, let alone *aim to bridge this gap*. ***The aim of this thesis was to directly contrast tests of a) decision-making and b) stimulus-response learning functions, interleaved with one another in the same experimental paradigm, and in the same participants to directly***

investigate the cognitive function(s) of DS particularly and of VS secondarily. Resolving this discrepancy in the literature is of high importance because DS is impaired in many disease states including PD and OCD, as well as many others.

Studies that suggest DS is a learning region often confound learning and decision-making. In many learning situations, decisions are made and feedback is provided to update decision accuracy. In behavioural tasks, learning is often measured by accuracy of the decisions. However, deficits in either learning from feedback or decision-making can yield impaired performance. Secondly, in many fMRI experiments, decision-making and feedback-based learning are modelled together and all active brain areas are ascribed a role in learning. Few studies attempt to separate decision-making from learning, which has perpetuated these discrepant views regarding DS's role in cognition. Consistent with our findings here, investigations that examine these processes separately have shown that DS, caudate nucleus (Nole M. Hiebert et al., 2014), putamen (Lam et al., 2016), or both (Francois-Brosseau et al., 2009), are recruited during decision-making and not learning.

Upon closer review of the theories implicating DS in learning described in Chapter 1, considering common methodological confounds and the division of the striatum into DS and VS, each of these models can recast the role of DS as a decision-making region.

5.1.1 DMS- and DLS-mediated Decision Making

DMS- and DLS-mediated learning theories were originally proposed in the rodent literature with some corroboration in homologous regions in humans. To reiterate, goal-directed learning is often ascribed to DMS, whereas DLS is purported to mediate habit learning. In humans, this takes the form of learning behaviours to the point of automaticity. VS, including NAcc, activity is clearly modulated by reward and there is strong evidence that this brain region mediates early stimulus-response learning. Our research suggests that DMS and DLS mediate decision making. Experiments in which DMS is lesioned in rodents often report the abolishment of goal-directed learning, leading to a release of habitual behaviours (Hernandez, Redgrave, & Obeso, 2015; Liljeholm & O'Doherty, 2012; Macpherson, Morita, & Hikida, 2014; Redgrave et al., 2010; Voorn, Vanderschuren, Groenewegen, Robbins, & Pennartz, 2004). Nishizawa et al. (2012) conducted a stimulus-

response learning task involving auditory stimuli and lever-press responses for a food pellet reward in rats. The task consisted of two phases. Phase 1 involved learning to associate a lever (either right or left) with a specific auditory tone, one tone for each lever. All rats were trained until a performance accuracy of at least 80% was reached. Once performance accuracy reached greater than 80%, regions of the striatum were lesioned and after seven days, Phase 2 was completed. In Phase 2, rats were required to perform the same stimulus-response learning trials as Phase 1. Lesions of DLS resulted in significantly reduced decision making accuracy during Block 1 of Phase 2. Towards the end of Phase 2, DLS-lesioned rats regained decision making accuracy comparable to control rats. On a subset of rats, a second lesion was carried out either in DMS or NAcc and then Phase 2 was conducted. Dual DLS and DMS lesions resulted in similar decision making trajectories, with significantly more errors early on and accuracy gradually increasing towards the end of Phase 2. On the other hand, dual DLS and NAcc lesions resulted in impaired decision making that did not improve across Phase 2. When all areas of DS were lesioned, decision making performance was impaired and never improved irrespective of new training. Associations could be re-learned through an intact NAcc, however, with response-selections potentially being taken over by different parts of the striatum following a lesion. This would be supported by the fact that dual DLS and DMS lesions, even when NAcc was spared (i.e., re-learning and new learning was possible), accurate performance of lever selections related to tones could not be regained.

In a study that examined DLS-mediated habit learning in humans using fMRI, Tricomi, Balleine, and O'Doherty (2009) found that an area of the putamen, that authors defined as DLS, was more active in participants who underwent habit learning compared to those whose learning remained goal-directed. The authors concluded that this area of the striatum is specifically involved in stimulus-response habit learning. These results would directly challenge our findings in Chapter 4 and our overall notions regarding DS's role in cognition. Upon closer examination of Tricomi et al., (2009), however, the area that was specifically preferentially activated in habit learning was actually located in a region of the ventral putamen that based on a number of approaches for distinguishing DS from VS would be considered a region of VS (Di Martino et al., 2008; Nole M. Hiebert et al., 2014; Jung et al., 2011; Kwak, Müller, Bohnen, Dayalu, & Seidler, 2012; P. A. MacDonald &

Monchi, 2011; Morris et al., 2012; Postuma & Dagher, 2006). Depending on the definition that you have adopted for DS versus VS, these results could alternatively be interpreted as evidence that VS mediates late-stage habit learning.

5.1.2 COVIS and SPEED Model

COVIS and SPEED, two models proposed by Gregory Ashby (Ashby, 1998; Ashby, Ennis, & Spiering, 2007; Ashby, Turner, & Horvitz, 2010), aim to explain the neural correlates of early category learning, and category learning moving towards automaticity, respectively. To reiterate, the COVIS model suggests that stimulus-response learning—specifically category learning—involves two competing systems, (1) a verbal system that classifies stimuli into verbalizable categories, and (2) an implicit system that uses procedural learning (Ashby, 1998). Both learning systems intersect with DS, and it is here where the competition takes place. In any categorization task, Ashby (1998) contend that only one of the two systems will dominate and the DS is responsible for mediating and switching between the two systems, and more importantly, it is suggested that *the DS mediates the stimulus-response association learning*. SPEED, on the other hand, postulates that the role of DS is to a) acquire stimulus-response associations and b) train cortical-cortical connections between higher order sensory and pre-motor areas (Ashby et al., 2007; Helie, Roeder, & Ashby, 2010; Soto, Waldschmidt, Helie, & Ashby, 2013). The theory maintains that the head of the caudate nucleus mediates early learning (COVIS), and as the associations become more practiced, progressing toward automaticity, more posterior regions of the striatum, namely the body and tail of the caudate nucleus, are purported to underlie late stage learning (SPEED). According to the SPEED account, once automaticity has been achieved, involvement of dorsal caudate nucleus ceases, and stimulus-specific, automatic behaviours become mediated by cortical regions (i.e. pre-motor, motor and visual cortices; Ashby, et al., 2007). The experimental data that are cited as support for these theories a) only consider neural activity in stimulus-response events, neglecting a feedback event (DeGutis & D’Esposito, 2007; Helie et al., 2010; Soto et al., 2013), or b) combine neural activity in stimulus-response and feedback events (Milton & Pothos, 2011; Nomura et al., 2007). Helie et al. (2010) investigated neural substrates of automatization of responses in a rule-based categorization learning paradigm that included over 10,000

trials, across 20 separate learning sessions, with fMRI data obtained in Sessions 1, 4, 10, and 20. They found that activity in DS was increased throughout Session 1, at the end of which high levels of response accuracy were ultimately achieved (i.e., 89.6%). In subsequent sessions, DS activity was significantly attenuated (i.e., after Session 1) whereas cortical activation continued to correlate with accurate categorization performance events, even after extensive training. Only stimulus-response or decision-making events (i.e. time period from the onset of the stimulus to the button-press response) were examined. Consistent with our claims, DS activation at the time of response selection and enactment could have arisen due to its involvement in decision-making processes that still require deliberation and not with association learning *per se*.

5.1.3 Actor-Critic Model

To reiterate, the actor-critic model states that stimulus-response learning consists of two separate components, a *critic* (i.e. the learner) which utilizes feedback to learn to predict future rewards, and an *actor* (i.e. the selector) which uses the information from the *critic* to make better decisions (O'Doherty et al., 2004; Sutton & Barto, 1998). O'Doherty et al. (2004) scanned healthy participants using 3T MRI while they completed two versions of a stimulus-response learning task, one instrumental and the other Pavlovian. The rationale for using an instrumental and Pavlovian task was to examine value predictions by the *critic* in the presence (i.e. instrumental task) and absence (i.e. Pavlovian task) of action selections by an *actor*. The results showed that VS correlated strongly with the prediction error signal in both tasks, whereas DS correlated with prediction error only during the instrumental task. Authors concluded that VS is the *critic*, coding for the prediction error signal and sending this information to the DS, or *actor*, where this information is used *to learn the stimulus-response association and perform rewarding future responses*. In other words, VS is implicated in reward processing and motivation and DS is implicated in stimulus-response learning *and* decision-making. Our interpretation is that VS, named their critic, is responsible for stimulus-response learning and DS, the actor, mediates decision making. In O'Doherty et al. (2004), the critic appears when feedback is presented, and received and processes feedback (i.e. learning), and the actor, is recruited prior to the response (i.e. during decision making).

With each of these models, the lack of agreement and/or distinction between DS and VS, as well as not separately examining decision making and learning, leads to confounds and controversies in the literature. The aim of this thesis was to unite two opposing literatures implicating DS in learning versus decision making by discussing how many studies that implicate DS in learning may actually be doing so erroneously, and rather the function that DS is mediating is decision making.

5.2 The role of VS in stimulus-response learning

Initially, VS was considered a region specialized for reward learning and processing (Camara et al., 2010; Cools et al., 2002; Delgado et al., 2000; Delgado, 2007; Knutson and Cooper, 2005; O'Doherty, 2004; Preuschoff et al., 2006; Sesack and Grace, 2010). However, some recent studies implicate VS in learning situations that are devoid of reward, punishment, or any feedback at all, challenging this specialization (Feigin et al., 2003; Ghiladri et al., 2007; MacDonald et al., 2011; Reiss et al., 2005; Seo et al., 2010; Shohamy et al., 2004; Shohamy et al., 2006; Tremblay et al., 2010). The results from Chapter 2 and 3 support this view.

5.3 Functions of DS and VS in Cognition

Our research refutes DS's role in learning, assigning it a function in selection and decision making. Further, our findings suggest that VS mediates stimulus-response learning. Review of cytoarchitectural distinctions as well as dissimilarities in connectivity of DS and VS, explain how these regions are adapted to these different functions. MSNs within DS have a much higher dopamine turnover rate compared to VS. Specifically, DS MSNs have a higher concentration of dopaminergic afferents, as well as of DAT compared to VS. A large number of dopaminergic afferents results quickly in high amplitude stimulation, whereas elevated DAT, responsible for synaptic clearance of dopamine, causes rapid drops in synaptic dopamine (Wickens, Horvitz, Costa, & Killcross, 2007). The anatomical makeup of DS, with high concentrations of dopaminergic afferents and DAT, results in brief dopamine stimulation periods, almost binary (i.e., off or on) responding, with maximal stimulation achieved quickly, across a wide range of dopamine firing frequencies,

followed by rapid clearance of synaptic dopamine (Zhang et al., 2009). These characteristics suit the DS to functions such as choosing between alternatives and decision making. VS, on the other hand, consists of much smaller MSNs with more widely-spaced dendritic spines, lower concentration of both dopaminergic innervation and DAT. Accordingly, dopaminergic pulses stimulate VS much more slowly, for longer periods of time, and with more variable intensity compared to DS (Wickens et al., 2007). These attributes are well suited to associating events or stimuli over time, for example in stimulus-response learning.

Secondly, the distinct cortical and limbic connections to DS and VS support their respective roles in decision making and learning. DS reciprocally connects to the primary, supplementary, and pre-motor cortex, as well as to the dorsolateral prefrontal cortex (DLPFC), parietal association cortex, and somatosensory cortex (Leh, Chakravarty, & Ptito, 2008). These cortical regions are largely effector areas as well as regions that aid in resolving response conflict, making DS ideally situated to perform functions such as deciding among alternatives and response selections. Particularly, DS is implicated in decisions that require deliberation (DeGutis & D'Esposito, 2007). Deliberation manifests as DS a) disinhibits the cortical regions representing the correct stimulus-response association and b) inhibits activity in cortical regions representing alternative stimulus-response associations (Ashby et al., 2007; Helie et al., 2010). Deliberation decreases as the strength of cortical-cortical connections increases to the point that they no longer require DS to facilitate them and inhibit alternative stimulus-response connections. We contend that stimulus-response automaticity is achieved when these selections become independent of DS.

VS, on the other hand, is reciprocally connected to regions associated with encoding such as the hippocampus, amygdala, anterior cingulate, as well as to orbitofrontal (OFC), ventrolateral prefrontal cortex (VLPFC), and anterior temporal and insular cortices (Kincaid, Zheng, & Wilson, 1998). VS projects directly to DS and has significant projections to VTA and SNc. VS is ideally suited for stimulus-response learning. Connections between cortical representations of stimuli and of responses are learned and also strengthened by VS. Projecting directly, and via spiraling connections through VTA

and SNc, to DS, VS biases DS to select particular responses (Haber, 2014; 2016; Choi et al., 2017). When the consequence of a stimulus-response sequence is rewarding, represented neurally by a dopaminergic pulse in VTA to VS, VS strengthens this connection. When the consequence is negative, represented by silencing of dopaminergic neurons in VTA projecting to VS, VS lessens connections. As stimulus-response-outcome associations becomes well-learned, VTA responding becomes neutral unless there is a violation of this expected pattern at which time new learning that implicates the VS begins again.

Synthesizing the above paragraphs with our results from Chapters 2-4 below, we outline our proposed model for the flow of information from novel stimuli and responses, to the establishment of stable, automatic stimulus-response pairings. In the formation of stimulus-response associations, DS and VS are points of convergence between extra-striatal regions and serve to link and facilitate connections between far reaching cortical areas. Prefrontal cortical areas, specifically the ventrolateral prefrontal and orbitofrontal cortices seem to be involved in storing stimulus-response pairings in working memory, and storing outcome and motivational information, respectively (Boettiger & D'Esposito, 2005; Choi, Ding, & Haber, 2017). VS serves as the hub for this information, and when the correct action is performed and subsequently rewarded, a phasic dopamine signal is sent from VTA to VS and evidence suggests that this influx of dopamine begins to facilitate connections between VLPFC and OFC through long term potentiation (Choi et al., 2017). Therefore, this suggests that VS is instrumental in enabling the learning of stimulus-response associations. In Chapters 2 and 3, activity in VS peaked early on when stimulus-response associations were first being formed. Additionally, high baseline dopamine levels, as in the case of patients with OCD and PD patients tested in the ON state, impaired learning, likely via impairments in the phasic dopamine response in VS.

Early in learning, DS is not biased in its selections and only becomes so with input from VS. This bias can only occur once stimulus-response associations are beginning to be learned, typically in later blocks of stimulus-response learning, as evidenced in Chapter 4. Input from VS comes in the form of reciprocal, spiraling, feedforward loops that link VS and DS through the dopaminergic midbrain (Haber, 2014). The increase in VS activity is

transmitted through VTA/SNc and facilitates a dopaminergic pulse to DS. While the stimulus-response association is being practiced, there are reports that DLPFC monitors the relations and goal-relevant information (i.e. changes in outcomes) and is attuned to stimulus-response ambiguities (Barber, Caffo, Pekar, & Mostofsky, 2013; Blumenfeld, Nomura, Gratton, & D'Esposito, 2013). This information in DLPFC, along with the learned response biases from VS, converge in DS and are used in decision making carried out by reciprocally connected effector regions such as, premotor, supplementary motor, and primary motor cortices (Barber et al., 2013; Blumenfeld et al., 2013; Haber, 2014). As practice continues and the response requires less and less consideration, the influence of DS on cortical areas storing the stimulus, response gradually lessens. Finally, as deliberation ceases, cortical-cortical connections are strengthened to the point where they can operate in the absence of DS, as supported in Chapter 4 (Ashby et al., 2007; Helie et al., 2010; N. M. Hiebert, Owen, Seergobin, & MacDonald, 2017).

5.4 Implications for PD

Cognitive dysfunction is an undisputed symptom of PD that leads to significant impairment in quality of life (Barone et al., 2009; Schrag et al., 2000). The etiology of cognitive impairments in PD is complex, but it is now clear that at least a subset of these symptoms arise from dysfunction of the striatum itself (Ray and Strafella, 2012). In PD, DS-mediated functions are compromised at baseline, and improved by dopamine replacement therapy. Conversely, VS functions are relatively spared off medication, and worsened by dopaminergic therapy, most notably at early stages of the disease (MacDonald and Monchi, 2011). Understanding VS- and DS-mediated cognitive functions, therefore, informs at least some cognitive symptoms in PD, and has implications for treatment. Currently, dopaminergic therapy is titrated to relieve DS-mediated motor symptoms, without taking into account the potential overdose of VTA-innervated regions. Ultimately, this greater understanding will prompt clinicians to formulate medication strategies that consider both motor and cognitive symptoms, as well as individual patient needs.

5.5 Implications for OCD

The role of the striatum in OCD is only starting to be elucidated and studies like Chapter 3 aim to clarify the specific roles of DS and VS. The results from Chapter 3 indicate that patients with OCD have task-related reductions in DS and VS function shown with corresponding behavioural and fMRI measures. In contrast, at rest or baseline, high baseline VS and low basal DS activity occurred relative to healthy controls. When performing stimulus-specific responses in a stimulus-response learning task, patients with OCD were impaired both during decision making and learning. Therefore, too low and too high activity both yielded the same result; impaired function.

With respect to symptomatology, Chapter 3 results support a role of VS in compulsive behaviours, specifically those patients with high baseline VS activity score lower on the compulsions sub-score of the YBOCS. To reiterate, the YBOCS is designed to characterize the presence and severity of obsessions and compulsions in patients with OCD (Kim, Dysken, & Kuskowski, 1990). Evidence suggests that OCD may be characterized by a dysfunctional reward system, reacting strongly to symptom-provoking stimuli and the completion of compulsive actions, but blunted responses to natural rewards (Figeet et al., 2016; Figeet et al., 2011). Within the OCD population, Chapter 3 results suggest that if baseline VS is too high, completion of compulsions is seen as less rewarding in these patients. The VS operates through graded potentials stimulated by dopamine dopaminergic neurons in the VTA (Wickens et al., 2007; Zhang et al., 2009). Typically, the dopaminergic pulse increases activity above baseline in VS to signal the receipt of a reward (Wolfram Schultz, 1998, 2015; W. Schultz, Apicella, Scarnati, & Ljungberg, 1992). In patients with OCD, the high baseline VS activity potentially obscures the positive graded potentials that result from natural rewards, or even from the rewarding experience of anxiety reduction that temporarily follows enactment of a compulsive behaviour (Figure 5.1). In this way, high baseline VS impairs learning, as well as the experience of natural and even maladaptive rewards (Figeet et al., 2016; Figeet et al., 2011).

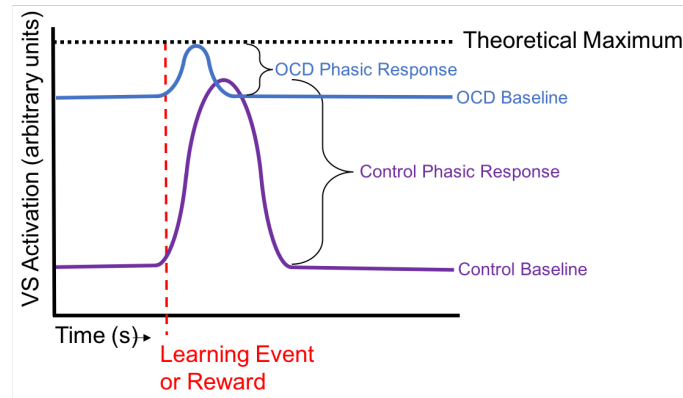


Figure 5.1 Theoretical effect of VS hyperactivity on reinforcing actions.

There is evidence to suggest the VS is hyperactive at rest in patients with OCD compared to healthy controls. This high baseline VS activity impairs the patient's ability to respond to phasic dopaminergic pulses leading to impaired reinforcement learning. In healthy controls, receiving a reward is followed by a burst of dopamine sent from the VTA to VS leading to a phasic rise in VS activity (purple line). The large magnitude phasic increase results in reinforcement learning and subsequently the healthy control will choose that response again. In OCD patients (blue line), the high baseline VS activity leaves little room for the phasic increase in activity, and the result may be impaired reinforcement learning. Clinically, performing compulsions may result in a phasic dopamine release into VS, reinforcing the action and making it more likely to be completed in the future. OCD patients that do not suffer from strong compulsions may have a high baseline VS compared to OCD patients with compulsions, and the even more diminished phasic response could result in unrewarded compulsive actions that do not continue.

The role of dopamine in OCD is currently an active area of research with much left to understand. This elucidation could lead to alternative treatments for OCD. As stated previously, SSRIs are the gold standard in treating OCD, pharmacologically. Typically SSRIs are prescribed as an adjunct therapy to CBT (Hirschtritt, Bloch, & Mathews, 2017). SSRIs method of action points to reducing symptoms of anxiety and depression related to OCD symptoms by raising the synaptic level of serotonin (Insel, 1981), and may not specifically be addressing the mechanisms of OCD symptoms, namely striatal deficits. Indeed, approximately 30-40% of OCD patients do not respond to current therapies (Atmaca, 2016), supporting the contention that current therapies may not be treating the core deficits of the disorder. In Chapter 2, it was determined that exogenous dopamine can simultaneously increase neural signal in DS and attenuate neural signal in the VS. Considering the baseline hypoactivity of DS and hyperactivity of VS at baseline in OCD,

this presents the intriguing possibility that exogenous dopamine might be helpful in bolstering DS, and perhaps decision making, response inhibition, and behavioural flexibility, while simultaneously diminishing the pathological hyperactivity in VS that seems related to obsessional thought (Rauch, Jenike, Alpert, & et al., 1994). There have been only very few studies investigating dopaminergic therapy in treating OCD (Ceccherini-Nelli & Guazzelli, 1994; Stryker et al., 2014). Ceccherini-Nelli and Guazzelli (1994) administered bromocriptine, a dopamine agonist, in four patients with treatment refractory OCD. Three out of the four saw dramatic improvements in OCD symptoms. Delle Chiaie, Scarciglia, Pasquini, Caredda, and Biondi (2011) tested the efficacy of aripiprazole, an atypical antipsychotic and partial dopamine agonist, as an adjunct to SSRI or clomipramine therapy in treatment-resistant OCD patients. 20 subjects completed the 12-week study and at the end of the study, authors saw a significant reduction in YBOCS scores in 18/20 patients. The authors conclude that the partial agonism of dopamine receptors can aid in the treatment of OCD patients who are resistant to SSRI monotherapy (Delle Chiaie et al., 2011). Further research into this area is warranted and a direct follow up of this is planned presently.

5.6 Limitations

There are several limitations in Chapters 2-4. Firstly, it is difficult recruiting and testing representative samples of patient populations, and ensuring control groups are adequately matched. Patients with neurological or psychiatric disorders are highly variable, both in terms of severity of the disease and co-morbidities. In Chapters 2 and 3, several steps were taken to reduce the variability due to noise between patients to facilitate accurate conclusions drawn from the data. Patients tested must: 1) be diagnosed with the disease of interest by a licensed physician, 2) be free of other neurological and psychiatric disorders or other serious health concerns, 3) not taking cognitive-enhancing medications, and 4) have no history of abusing alcohol, prescription medications or illegal drugs. Additionally, control participants were age- and education-matched to patients, and had similar scores on measures of cognitive health, such as MoCA, ANART, and verbal fluency. Recruiting control participants that match on as many different aspects as possible yields more

defendable results. In all experiments, these standard measures of cognitive health were used to ensure all participants were cognitively intact, and able to complete the experiment.

Secondly, the spatial resolution of the neuroimaging data creates difficulty in understanding fully the functional specificity of different brain regions. Brain tissue contains many different small structures, such as receptors, neurons, and support cells, and 3T neuroimaging is unable to differentiate these structures or understand how they work together to perform specific functions. For example, in each of the studies the voxel size was 2.5 mm^3 which is orders of magnitude larger than single neurons. Therefore, imaging each voxel averages across many structures and neurons. There are many tradeoffs when parameters are chosen for neuroimaging experiments. Decreasing the size of the voxels can grant increased spatial resolution, but it also increases the total number of voxels as well as the number of brain slices required to capture the whole brain. This results in a decreased temporal resolution because it requires a much longer TR (i.e. the time required to take one whole-brain picture). The voxel size chosen in this thesis and the corresponding TR maximizes spatial and temporal resolution in the experiments.

Lastly, fMRI is correlational in nature and generally it is difficult to establish or claim true causality. To reiterate, fMRI examines changes in blood flow and not neuronal activity. Action potentials require a significant amount of energy in the form of oxygen and glucose and because neurons are unable to efficiently store these molecules, they must be obtained from oxygenated blood (Yablonskiy & Haacke, 1994). As a result, when a neuron fires, an increase in deoxygenated blood surrounds the neuron to facilitate the action potential, causing an influx of oxygenated blood, and it is this change in blood flow that is imaged in fMRI (Yablonskiy & Haacke, 1994). This concept is almost wholly accepted in the neuroimaging community and causality is often inferred from BOLD changes. Nevertheless, pharmacological manipulation in a disease state such as PD facilitates stronger inferences. The neuropathology of PD and the effect of dopaminergic therapy on patients with PD is well-understood and this knowledge is combined with the neuroimaging results. For example, it is understood that DS is dopamine deplete and impaired at baseline and dopamine administration remediates this impairment. If decision-making performance is impaired at baseline and improved with dopamine therapy, along

with an increase in BOLD signal in DS, it can be said with more certainty that DS mediates decision making.

5.7 Conclusions

We completely refute the prevalent contention that DS mediates early (Boettiger & D'Esposito, 2005; Brovelli, Laksiri, Nazarian, Meunier, & Boussaoud, 2008; Delgado, Miller, Inati, & Phelps, 2005; Foerde, Knowlton, & Poldrack, 2006; Brian Lau & Glimcher, 2007; B. Lau & Glimcher, 2008; R. A. Poldrack, Prabhakaran, Seger, & Gabrieli, 1999; Thompson, 1959; Thompson RL, 1963; Xue, Ghahremani, & Poldrack, 2008), and late-stage, learning with or without feedback (Helie et al., 2010; R. A. Poldrack et al., 2005; Soto et al., 2013; Yamamoto, Kim, & Hikosaka, 2013; Yin & Knowlton, 2006). Our research suggests rather that VS mediates early stimulus-response learning. In contrast, our findings strongly support a role for DS in decision making (Atallah, Lopez-Paniagua, Rudy, & O'Reilly, 2007; Nole M. Hiebert et al., 2014; Brian Lau & Glimcher, 2007; B. Lau & Glimcher, 2008; Liljeholm & O'Doherty, 2012; A. A. MacDonald et al., 2014; P. A. MacDonald & Monchi, 2011; Smittenaar et al., 2012; Wunderlich, Dayan, & Dolan, 2012), when there is ambiguity, and deliberation is required (Ali, Green, Kherif, Devlin, & Price, 2010; Cools & D'Esposito, 2011; Daniel et al., 2010; DeGutis & D'Esposito, 2007; P. A. MacDonald et al., 2011; Ohira et al., 2010; Robertson, Hiebert, Seergobin, Owen, & MacDonald, 2015).

DS is a region implicated in many disorders ranging from Parkinson's disease, obsessive-compulsive disorder, and addiction. Elucidating the function(s) of DS is integral to developing cognitive and symptom profiles of these diseases, as well as in identifying and understanding new targets for therapy and potentially new therapeutic approaches.

5.8 References

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Appendices

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Appendix B Ethics Approval Notice from the University of Western Ontario



Western
Research

Date: 30 November 2017

To: Penny MacDonald

Project ID: 102018

Study Title: Distinguishing the roles of ventral and dorsal striatum in cognition (REB #18517)

Application Type: Continuing Ethics Review (CER) Form

Review Type: Delegated

Full Board Reporting Date: December 5, 2017

Date Approval Issued: 30/Nov/2017

REB Approval Expiry Date: 29/Nov/2018

Dear Penny MacDonald ,

The Western University Research Ethics Board has reviewed the application. This study, including all currently approved documents, has been re-approved until the expiry date noted above.

REB members involved in the research project do not participate in the review, discussion or decision.

Western University REB operates in compliance with, and is constituted in accordance with, the requirements of the TriCouncil Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2); the International Conference on Harmonisation Good Clinical Practice Consolidated Guideline (ICH GCP); Part C, Division 5 of the Food and Drug Regulations; Part 4 of the Natural Health Products Regulations; Part 3 of the Medical Devices Regulations and the provisions of the Ontario Personal Health Information Protection Act (PHIPA 2004) and its applicable regulations. The REB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000940.

Please do not hesitate to contact us if you have any questions.

Sincerely,

Kelly Patterson, Ethics Officer, on Behalf of Dr. Joseph Gilbert, HSREB Chair

Note: This correspondence includes an electronic signature (validation and approval via an online system that is compliant with all regulations).

Curriculum Vitae

Post-secondary Education and Degrees

2014 – 2018	Doctor of Philosophy , Physiology and Pharmacology, University of Western Ontario – May 2018 Supervisors: Dr. Penny MacDonald and Dr. Adrian Owen Thesis title: <i>Role of dorsal striatum in learning and decision-making</i>
2012 – 2014	Master of Science , Physiology and Pharmacology, University of Western Ontario – May 2014 Supervisors: Dr. Penny MacDonald and Dr. Adrian Owen Thesis title: <i>Functional role of the striatum in stimulus-response learning: evidence from functional MRI and patients with Parkinson's disease</i>
2008 – 2012	Bachelor of Medical Science , Honors Specialization in Physiology with distinction, University of Western Ontario – June 2012

Honors, Scholarships and Awards during university:

2018	Canadian Association for Neuroscience Annual Meeting Travel Award – \$750
2017	Harold Brett Memorial Fellowship in Neuroscience – \$1200
2016	George W. Stavaky Teaching Scholarship – Value \$1000 and a funded teaching assistantship for the 2017-2018 academic year
2016	Graduate Student Teaching Award for the Department of Physiology and Pharmacology – Value \$500
2016	Natural Sciences and Engineering Research Council – Alexander Graham Bell Canadian Graduate Scholarship – Value \$70,000
2014 – 2016	Ontario Graduate Scholarship (Declined) – Value \$15,000
2014 and 2015	Jonathan and Joshua Memorial Graduate Scholarship in Mental Health Research – Value \$15,000
2014	Second Place in Neurosciences Division – Department of Physiology and Pharmacology Graduate Research Day – Value \$100
2008 – 2012	Dean's Honor List, University of Western Ontario

Teaching Experience during University

Sept. – Dec., 2012 – 2017	Teaching Assistant , University of Western Ontario Course Title: Physiology 4710: Physiology of the Senses <ul style="list-style-type: none"> Assisted the professor in ensuring the accuracy of lecture material. Reviewed and revised online quiz, and exam questions.
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- Held online and in-class tutorials, and one-on-one tutoring sessions for students.
- Created review session quizzes before midterm and final exams.
- Responded to student questions during tutorial and by email.
- Trained and assisted new teaching assistants in learning the material and conducting tutorials.
- Proctored midterm and final exams.

Research Experience:

- | | |
|----------------|---|
| 2014 – Present | <p>Doctoral Student, Department of Physiology and Pharmacology, University of Western Ontario</p> <ul style="list-style-type: none"> • PhD Project: Investigating striatal-mediated cognition using healthy participants and patients with striatal dysfunction (i.e., Parkinson's disease, Obsessive compulsive disorder, substance abuse, etc.) • Conducting behavioural and functional magnetic resonance imaging experiments involving: stimulus-response learning, implicit and explicit word learning, reversal learning, and cognitive control |
| 2012 – 2014 | <p>Master's Student, Department of Physiology and Pharmacology, University of Western Ontario</p> <ul style="list-style-type: none"> • Master's project: investigating the roles of the dorsal and ventral striatum in stimulus-response learning and decision-making using fMRI in healthy participants and patients with Parkinson's disease on and off dopaminergic medication. • Conducted additional behavioural and fMRI experiments involving: stimulus-response learning, implicit and explicit learning, working memory, as well as Stroop tasks. • Drafted a research proposal investigating the effect of genetic polymorphisms on cognition in patients with Parkinson's disease. • Drafted a research proposal investigating the effect of methylphenidate on cognition in patients with Parkinson's disease. • Wrote and revised research ethics approved by Health Sciences Research Ethics Board (HSREB) of the University of Western Ontario and the Ethics Review Board of the Sudbury Regional Hospital. |
| 2011 – 2012 | <p>Undergraduate Student, Department of Physiology and Pharmacology, University of Western Ontario</p> <ul style="list-style-type: none"> • Undergraduate thesis project: examining the effect of Bisphenol A on the expression of specific glucocorticoid-regulated genes in human syncytiotrophoblast cells |

- Researched and proposed a project examining the effect of reactive oxygen species on preadipocyte proliferation in rats

Publications, Presentations and Abstracts

Publications

Hiebert NM, Owen AM, Seergobin KN, and MacDonald PA. (2017) Dorsal striatum mediates deliberate decision making, not late-stage, stimulus-response learning. *Human Brain Mapping* 38(12): 6133-6156.

Hampshire A, Hellyer PJ, Parkin B, **Hiebert N**, MacDonald P, Owen AM, Leech R, and Rowe J. (2015) Network mechanisms of intentional learning. *NeuroImage* 127: 123-34.

Robertson BD, **Hiebert NM**, Seergobin KN, Owen AM, and MacDonald PA. (2015) Dorsal striatum mediates cognitive control, not cognitive effort *per se*, in decision making: An event-related fMRI study. *NeuroImage* 114: 170-184.

Hiebert NM, Vo A, Hampshire A, Owen AM, Seergobin KN, and MacDonald PA. (2014) Striatum in Stimulus-Response Learning via Feedback and Decision making. *NeuroImage* 101:448-457.

Hiebert NM, Seergobin KN, Vo A, Ganjavi H, and MacDonald PA. (2014) Dopaminergic Therapy Affects Learning and Impulsivity in Parkinson's disease. *Annals of Clinical and Translational Neurology* 1(10): 883-843.

Vo A, **Hiebert NM**, Seergobin KN, Solcz S, Partridge A, and MacDonald PA. (2014) Dopaminergic Therapy Impairs Learning but not Decision-making in Parkinson's disease. *Frontiers in Human Neuroscience* 8:784.

Presentations and Abstracts

Hiebert NM, Kahn AR, Naci L, Vo A, Wang BT, Owen AM, Seergobin KN, and MacDonald PA (2018, June) *Structural and functional biomarkers of Parkinson's disease: Using structural and functional neuroimaging to identify the presence and severity of Parkinson's disease*. Poster presentation at the CIHR Research Poster Presentation at the Canadian Student Health Research Forum, Winnipeg, Manitoba, Canada.

Hiebert NM, Khan AR, Vo A, Wang BT, Owen AM, Seergobin KN, and MacDonald PA (2018, May) *Biomarkers of Parkinson's disease: Striatal sub-regional structural morphometry and diffusion MRI*. Poster presentation at the 12th annual Canadian Association for Neuroscience, Vancouver, British Columbia, Canada.

Hiebert NM, Naci L, Owen, AM, and MacDonald PA (2018, May) *Functional Biomarkers of Parkinson's disease: Changes in brain-wide network connectivity in Default Mode and Frontal-parietal Control Networks*. Poster presentation at the 12th annual Canadian Association for Neuroscience, Vancouver, British Columbia, Canada.

Hiebert NM, Lawrence M, Watling M, Owen AM, Seergobin KN, and MacDonald PA (2018, April) *Role of baseline dorsal and ventral striatum activity in stimulus-response learning in patients with obsessive-compulsive disorder*. Platform presentation at the Department of Clinical Neurological Sciences Research Day, University of Western Ontario, London, Ontario, Canada.

Hiebert NM, Owen AM, Ganjavi H, Jenkins ME, Mendonça D, Seergobin KN, MacDonald and PA (2017, April) *Dorsal caudate nucleus mediates response selection and not feedback-driven stimulus-response learning*. Platform presentation at the Department of Clinical Neurological Sciences Research Day, University of Western Ontario, London, Ontario, Canada.

Hiebert NM, Khan AR, Vo A, Wang BT, Owen AM, Seergobin KN, and MacDonald PA (2017, April) *Biomarkers of Parkinson's disease: Striatal sub-regional structural morphometry and diffusion MRI*. Platform presentation at the Department of Clinical Neurological Sciences Research Day, University of Western Ontario, London, Ontario, Canada.

Gustainis RV, Seergobin KN, **Hiebert NM**, Vo A, and MacDonald PA (2017, April) *The Effects of Parkinson's Disease and Dopaminergic Medication on Driving Performance and Cognitive Measures*. Platform presentation at the Department of Clinical Neurological Sciences Research Day, University of Western Ontario, London, Ontario, Canada.

Hiebert NM, Owen, AM, Seergobin KN & MacDonald PA (2016, September) *The effect of dopaminergic therapy on stimulus-response learning and decision-making in Parkinson's disease using 3T MRI*. Poster presented at the 4th World Parkinson Congress, Portland, Oregon, United States of America.

Hiebert NM, Owen, AM, Seergobin KN & MacDonald PA (2016, May) *The effect of dopaminergic therapy on stimulus-response learning and decision-making in Parkinson's disease using 3T MRI*. Poster presented at the Canadian Association for Neuroscience conference, Toronto, Ontario, Canada.

Hiebert NM, Owen AM, Seergobin KN, & MacDonald PA (2015, March) *Does Dorsal Striatum Mediate Habit Learning or Decision-making?* Platform presentation presented at the Department of Clinical Neurological Sciences Research Day, University of Western Ontario, London, Ontario, Canada.

Robertson B, **Hiebert NM**, Seergobin KN, MacDonald PA. (2015, March) *Does the dorsal striatum mediate cognitive flexibility? An event-related functional MRI study*. Platform presentation at the Department of Clinical Neurological Sciences Research Day, University of Western Ontario, London, Ontario, Canada.

Hiebert NM, Owen AM, Seergobin KN, & MacDonald PA (2014, October) *Does Dorsal Striatum Mediate Habit Learning or Decision-making?* Poster presented at the Department of Physiology and Pharmacology Graduate Research Day, University of Western Ontario, London, Ontario, Canada.

Vo A, **Hiebert NM**, Seergobin KN, Solcz S, Partridge A, & MacDonald PA. (2014, July) *Dopaminergic medication impairs learning but not decision making in Parkinson's disease*. Poster presented at the 24th Annual Meeting of the Canadian Society for Brain, Behaviour, and Cognitive Science (CSBBCS), Ryerson University, Toronto, Ontario, Canada.

MacDonald PA, **Hiebert NM**, Vo A, Hampshire A, Owen AM, Ganjavi H, Seergobin KN. (2014, May) *Understanding the role of striatum in learning and decision-making using fMRI*. Presented at the 18th International Congress of Parkinson's Disease and Movement Disorders, Stockholm, Sweden.

MacDonald PA, Vo A, **Hiebert NM**, Seergobin KN. (2014, May) *Learning and decision making in Parkinson's disease*. Presented at the 18th International Congress of Parkinson's Disease and Movement Disorders, Stockholm, Sweden.

Robertson B, **Hiebert NM**, Seergobin KN, MacDonald PA. (2014, May) *Does the dorsal striatum mediate cognitive flexibility? An event-related functional MRI study*. Poster presentation at the Southern Ontario Neuroscience Association, London, Ontario, Canada

Hiebert NM, Vo A, Seergobin KN, Hampshire A, Solcz S, Owen AM and MacDonald PA. (2014, March) *The Roles of Dorsal and Ventral Striatum in Stimulus-Response Learning: Implications for Parkinson's disease*. Poster presentation at the Department of Clinical Neurological Sciences Research Day, University of Western Ontario, London, Ontario, Canada.

Robertson B, **Hiebert NM**, Seergobin KN, MacDonald PA. (2014, March) *Does the dorsal striatum mediate cognitive flexibility? An event-related functional MRI study*. Poster presentation at the Department of Clinical Neurological Sciences Research Day, University of Western Ontario, London, Ontario, Canada.

Robertson B, **Hiebert NM**, Seergobin KN, MacDonald PA. (2014, March) *Does the dorsal striatum mediate cognitive flexibility? An event-related functional MRI study*. Poster presentation at the London Health Sciences Research Day, London, Ontario, Canada

Vo A, **Hiebert NM**, Seergobin KN, Solcz S, Partridge A and MacDonald, PA. (2014, February) *Dopaminergic medication impairs learning but not decision making in Parkinson's disease*. Paper presented at 43rd annual meeting of the Lake Ontario Visionary Establishment (L.O.V.E), Niagara Falls, Ontario, Canada.

Hiebert NM, Vo A, Seergobin KN, Hampshire A, Solcz S, Owen AM and MacDonald PA. (2013, October) *The Roles of Dorsal and Ventral Striatum in Stimulus-Response Learning: Implications for Parkinson's disease*. Poster presentation at the 3rd World Parkinson Congress, Montreal, Quebec, Canada.

Vo A, **Hiebert NM**, Seergobin KN, Solcz S, Owen AM, Partridge A and MacDonald PA. (2013, October) *Recasting the role of dorsal striatum in learning and decision-making*. Poster and platform presentation at the 3rd World Parkinson Congress, Montreal, Quebec, Canada.

Leadership Experience during University

Sept. 2013 – May
2018

Senior Lab Member, Dr. Penny MacDonald's Lab
University of Western Ontario

- Assisted in the supervision of a three undergraduate and one medical student.
- Taught basic research methods such as proper data collection and data management, as well as more sophisticated methods such as collection and analysis of functional magnetic resonance imaging data.
- Reviewed and edited manuscripts and presentations before submission to supervisor.

May 2013 – May
2014

Society of Graduate Students Representative for the Physiology and Pharmacology Graduate Student Council,
University of Western Ontario

- Debate and vote on issues pertaining to the student body of the University of Western Ontario
- Disseminate information obtained at Society of Graduate Student meetings to the Physiology and Pharmacology Graduate Student Council